NOVEL 4-THIAZOLIDINONE DERIVATIVES AS α- AMYLASE INHIBITORY ACTIVITY: SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

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In partial fulfillment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-II – PHARMACEUTICAL CHEMISTRY

Submitted by

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OCTOBER – 2018

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"NOVEL 4-THIAZOLIDINONE DERIVATIVES AS α-AMYLASE INHIBITORY ACTIVITY: SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION"** submitted by the student bearing **Reg. No: 261615208** to The Tamil Nadu Dr. M. G. R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in the **DEPARTMENT OF PHARMACEUTICAL CHEMISTRY** was evaluated by us during the examination held on.....

Internal Examiner **External Examiner**

CERTIFICATE

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I further declare that, this work is original and has not been submitted in part or full for the award of any other degree or diploma in any other University.

Place: Kumarapalayam **Mrs. SWEETHA S.RANI**

Date: **Reg. No. 261615208**

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Mrs. SWEETHA S.RANI

Reg. No: (261515208)

DEDICATED

TO

MY FAMILY

AND GUIDE

CONTENT

1. INTRODUCTION

Chemistry is a very broad subject, and can justly claim to encompass many aspects of the study of biological molecules. To most researchers in the diabetic fields, the term 'chemistry' is often used in a much narrower way and is synonymous with the synthetic chemistry as a tool for the discovery of antidiabetic drugs.

1.1. PHARMACEUTICAL CHEMISTRY

Pharmaceutical Chemistry is an area of chemistry that deals with the structure, properties and reaction of compounds that contains carbon. Chemists in general and organic chemists in particular can create new molecules never before proposed which, if carefully designed, may have important properties for the betterment of the human experience. One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecule having value as human therapeutic agents[1].

The department of pharmaceutical chemistry is to impart in depth knowledge about all the chemical aspects of drugs and natural products, such as the structure, synthesis, isolation and structural activity relationship with the pharmacological activity.

Medicinal chemistry

Medicinal chemistry and bioorganic chemistry is concerned with the design, synthesis and analysis of the relationship between molecular structure and biological activity for compounds that can be used for the care or treatment of disease[1].

In medicinal chemistry, the chemist attempts to design and synthesis a medicine or pharmaceutical agent which will benefit humanity. Such a compound could be called as a 'drug'.

Medicinal chemistry is a part of pharmaceutical chemistry. Medicinal chemistry is discipline at the intersection of chemistry and pharmacology involved with designing, synthesizing and developing pharmaceutical drugs. Medicinal chemistry involves the identification, synthesis and development of new chemical entities suitable for therapeutic use. It also includes the study of existing drugs, their biological properties and their quantitative structure activity relationship (QSAR).

Medicinal chemistry is the application of chemical research techniques to the synthesis of pharmaceuticals. During the early stages of medicinal chemistry development, scientist were primarily concern with the isolation of the medicinal agents founds in plants. Today, scientists in this field are also equally concerned with creation of new synthetic drug compounds. Medicinal chemistry almost always geared towards drug discovery and development.

The first step is pharmaceutical focused on quality aspects of medicines and aims to assure fitness for the purpose of medicinal products. Medicinal chemistry is a highly interdisciplinary science combining organic chemistry with biochemistry, computational chemistry, pharmacology, pharmacognosy, molecular biology, statistics and physical chemistry. The second step of drug discovery involves the synthetic modification of the hits in order to improve the biological properties of the compound pharmacophore.

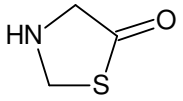
Heterocyclic chemistry is the chemistry branch dealing exclusively with synthesis, properties and application of heterocyclic. Heterocyclic compound is an organic compound that contains a ring structure containing atom in addition to carbon, such as sulfur, oxygen or nitrogen as part of the ring. They may be either simple aromatic

or non-aromatic rings some heterocyclic compounds are known as carcinogens. Researchers have showed that heterocyclic amines are the Carcinogenic chemicals.

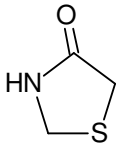
A heterocyclic compound is one which possesses a cyclic structure with at least two different kinds of hetero atoms in the ring. Nitrogen, oxygen and sulphur are most common hetero atoms. Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways.

1.2. THIAZOLIDINONE

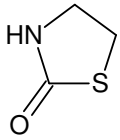
Thiazolidin-4-one occurs as yellow crystal and odorless. It is soluble in water, ethanol and solvent ether. Tetra hydro derivative of thiazole ring is known as thiazolidine[2-3].



5-Thiazolidinone



4-Thiazolidinone



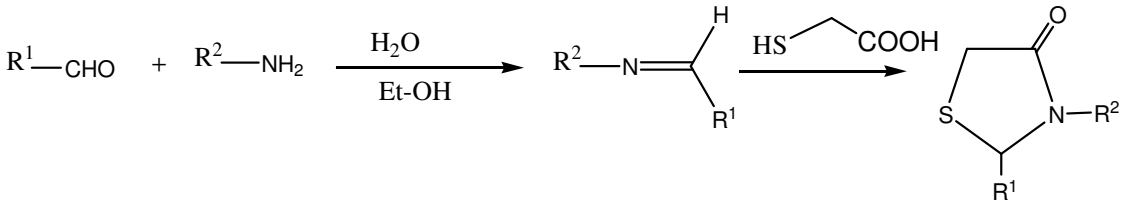
2-Thiazolidinone

4- thiazolidinone and its derivatives have high pharmacological relevance since they are available in both natural products and pharmaceutical compounds[4-8].

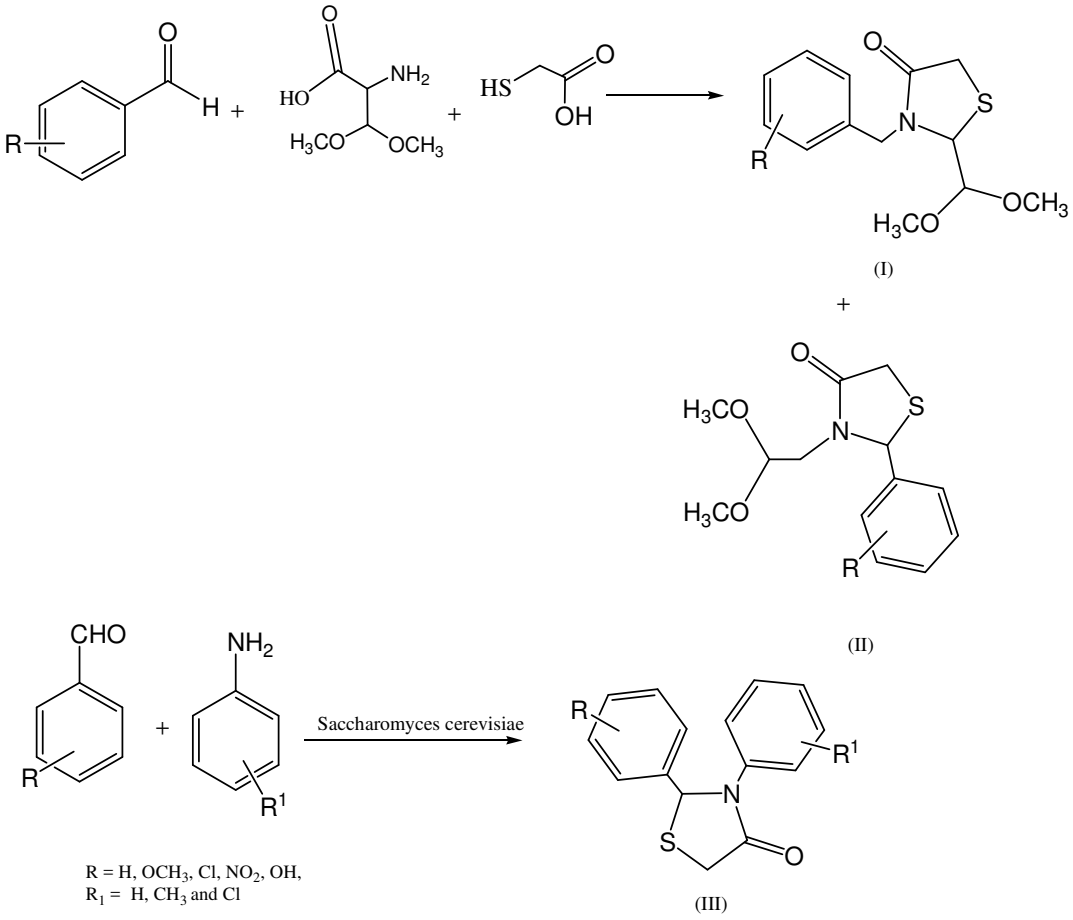
Method of preparation

The number of methods for the synthesis of thiazolidinones is widely reported in the literature. The main synthetic routes to thiazolidin-4-ones comprising three components such as an amine, a carbonyl group and mercapto acid. The classical method of synthesis reported may be either a one-pot three-component condensation method or a two-step process. The reaction starts by formation of an imine which undergoes attack by sulfur nucleophile, followed by intramolecular cyclization to eliminate water[9].

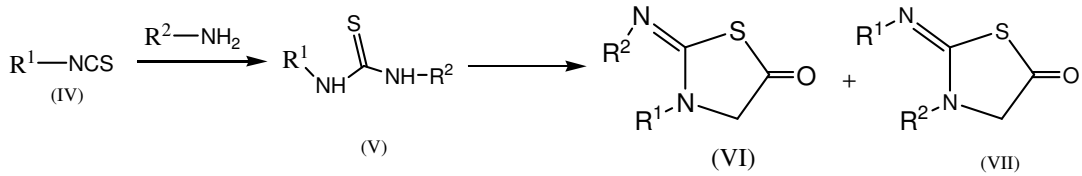
Kozlov co-workers[10] reported a one-step cyclization reaction wherein the reaction of ethyl 5-phenylthioureido-3-imidazole-4-carboxylate with bromoacetic acid gives an imidazolylimino thiazolidin-4-one. This cyclization reaction starts by one of the nitrogen atom of nucleophilic centers in 5-thioureido-3-imidazole-4-carboxylic acid derivative yields the desired thiazolidin-4-ones[11].

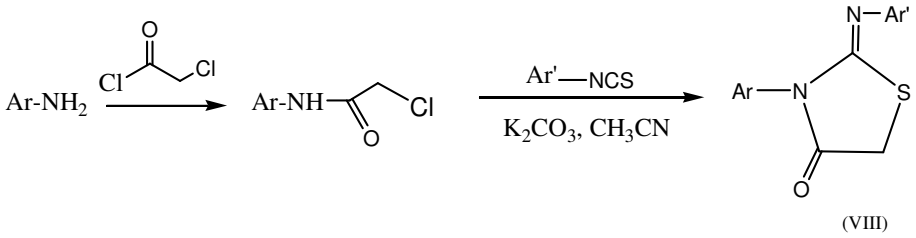


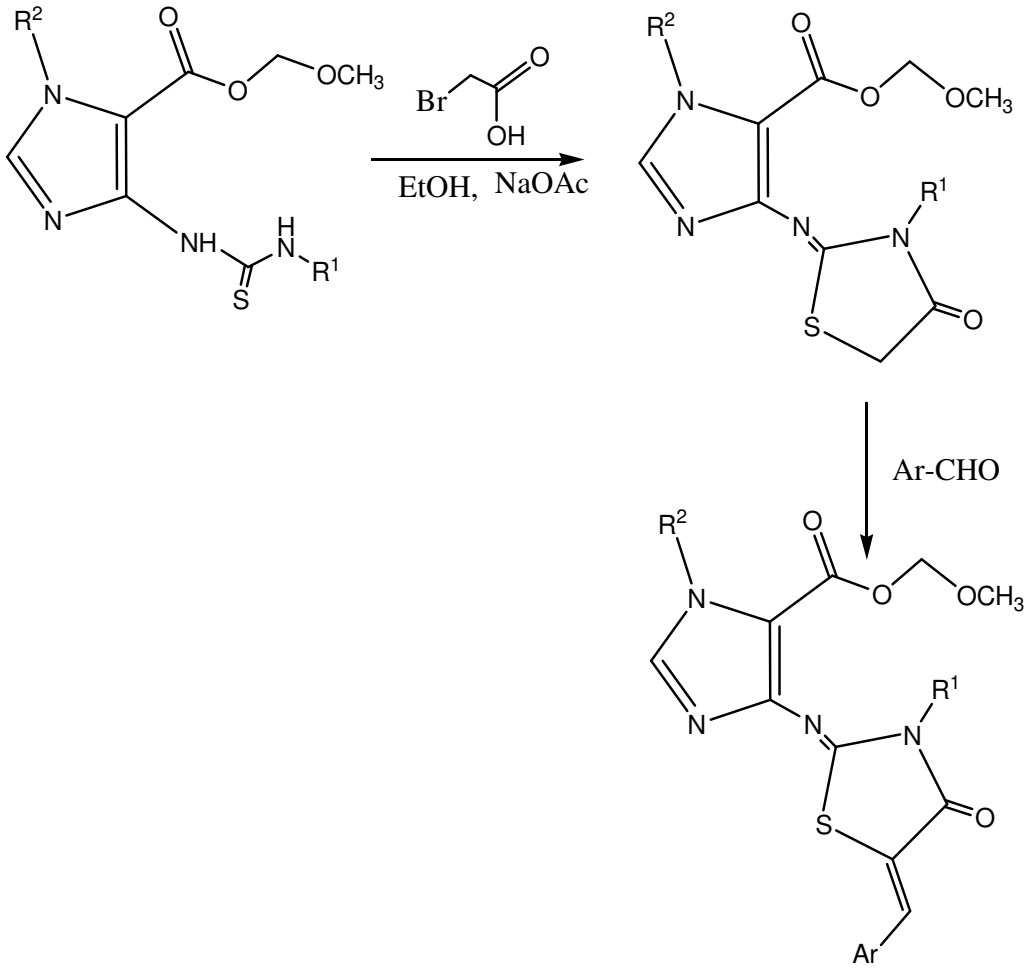
Further, new synthetic route for the preparation of 2-isopropyl-3-benzyl-1,3-thiazolidin-4-ones and 2-phenyl-3-isobutyl-1,3-thiazolidin-4-ones by using 1:1:3 ratio of valine, aldehyde and mercaptoacetic acid was reported by Cunico[12]*et al.,*., and suggested that the introduction of strong withdrawing group such as NO_2 present in benzaldehyde favored the synthesis of hetero-cycle (**I**) in good yields, whereas the methoxy and fluorogroups produces the type (**II**) thiazolidin-4-ones. In this connection a solvent-free synthesis of five-membered heterocyclic thiazolidin-4-ones from phenyl hydrazine and 2,4-DNP as an amino moiety[13]. Another method of preparation of 2,3-diaryl-thiazolidin-4-ones (**III**) was established, where *saccharomyces cerevisiae* enzyme also called as baker's yeast comprising lipase was used as a catalyst in this reaction and accelerated the formation of imines as well as cyclo-condensation reaction of aryl aldehydes, amines with thioglycolic acid.



Further, the reaction of alkyl or aryl isothiocyanate (**IV**) with a primary amine furnished the corresponding thiourea derivative (**V**), which directly undergoes cyclization reaction by treating with halo acetic acid to yield two isomers of 2-imino-thiazolidin-4-ones[14](**VI, VII**). In addition, coupling reaction between α-chloro amide derivatives with an isothiocyanate in the presence of a mild base such as K_2CO_3 afforded the iminothiazolidin-4-one derivatives[15] (**VIII**).

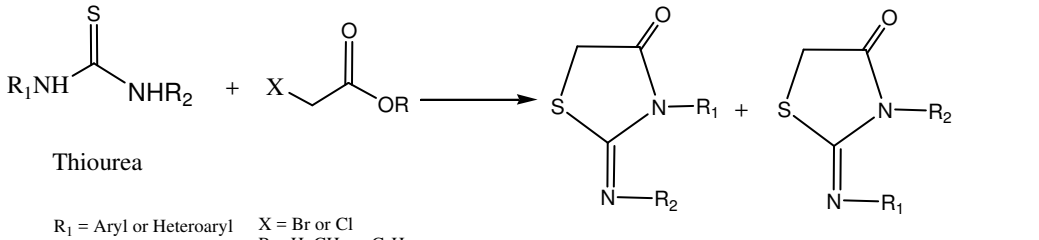

R1—NCS
(IV)
R2—NH2
(V)
(VI)
(VII)


Ar-NH2
Ar-NH
Cl
Ar'—NCS
K2CO3, CH3CN
Ar
(VIII)


OCH3
Br
OH
EtOH, NaOAc
Ar-CHO
Ar

Mechanism of reaction for the preparation of Thiazolidinones

The reaction between substituted thiourea with acid to haloacetic acid produces 2-iminothiazolidin-4-ones. These reactions occur in polar solvents such as ethyl alcohol under reflux and in the presence sodium acetate or pyridine[16]. Substituted thiourea can be procured by a reaction with primary amines. Thiourea undergoes asymmetric reactions and form two regioisomers, where the regioselectivity is controlled by electronic factors, especially the combination of electron-withdrawing substituent (aryl or heteroaryl) with nitrogen imino group[17].

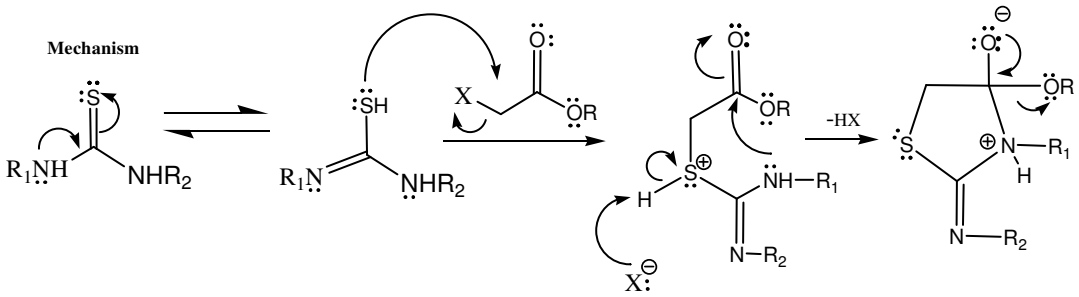


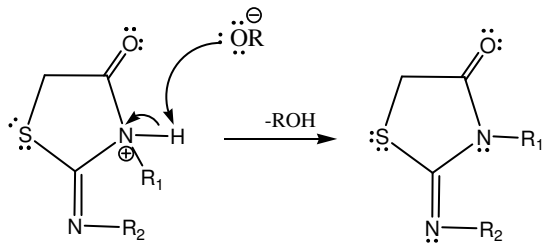
Thiourea

R_1 = Aryl or Heteroaryl X = Br or Cl
R = H, CH_3 or C_2H_5

R_2 = Alkyl

Mechanism





Properties of 4-thiazolidinones

The 4-thiazolidinones are generally solid forms, often melting with decomposition but the attachment of alkyl group with the nitrogen minimizes the melting point. The aryl or higher alkyl substituent's of 4-thiazolidinone slightly soluble in water.

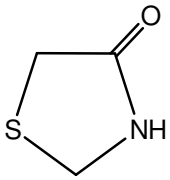
Chemical properties of 4-thiazolidinones

The structure of 4-thiazolidinones exists in the literatures[18]. 4-Thiazolidinones are the derivatives of thiazolidine with C=O group at fourth position[19]. Substitution of various groups at 2^{nd}, 4^{th} and 5^{th} position is possible. A different optical isomeric form of thiazolidinone is reported in the references[20] and number of regioselective isomers has been reported[21,22]. The C=O group of thiazolidin-4-one is highly inert nature. But in few cases thiazolidin-4-one on reaction with Lawesson's reagent gives corresponding thiazolidin-4-ones[23]. Tautomer of 2-iminothiazolidine-4-one found to exhibit some chemical interest.

Several methods are available in order to synthesis a thiazolidin-4-ones in the literatures[24] which involve conventional, microwave irradiation method and combinatorial synthesis. The reaction between NH_2 with CS_2 in the presence of alkali which then reacts with haloalkanoic acid in the presence of Na_2CO_3 yields thiazolidin-4-ones.

Among the various reactions involving the thiazolidin-4-one ring, reactions occurring at first position (sulfur) in the oxidation reaction[25], third position (nitrogen) in N–alkylation reaction[26] and mannich reaction[27], fourth position (C=O) in thionation reaction via Lawesson's reagent[28] and fifth position (CH_2) in condensation reaction with

aldehydes and ketones or diazonium salts[29] is processed. Here by all the above reactions are disussed in detail.



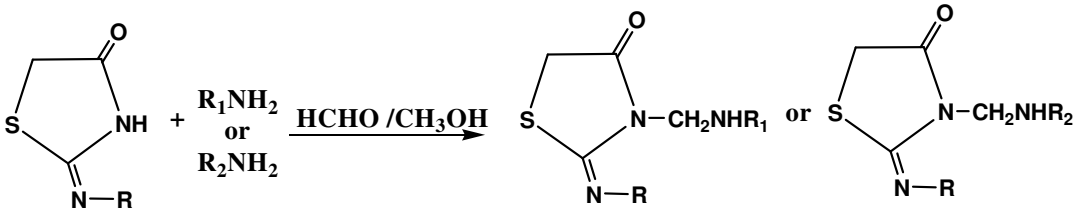
***N*–alkylation reaction**

Nishimoto and co-workers[30] found that thiazolidin-4-ones substituted in the second position with alkyl or alkoxy groups undergo an *N*-alkylation reaction. In this method, equivalent amount of potassium hydroxide was used with thiazolidin-4-ones in anhydrous DMF which promotes the formation of amide anion through the abstraction of hydrogen at N-3 position and subsequent attack of this anion with 1, 2-dibromoethane at room temperature. The use of potassium hydroxide is essential for the formation of amide anion, since thiazolidin-4-one unsubstituted in third position are weak acids.

***N*-2-bromoethyl-4-thiazolidinone**

Mannich reaction

Mannich reactions are generally occurring between 2-iminothiazolidin-4-ones and NH_2 or NH in presence of formaldehyde or paraformaldehyde in methyl alcohol to produce 2-imino-3-(substituted amino methyl) thiazolidin-4-one[31].

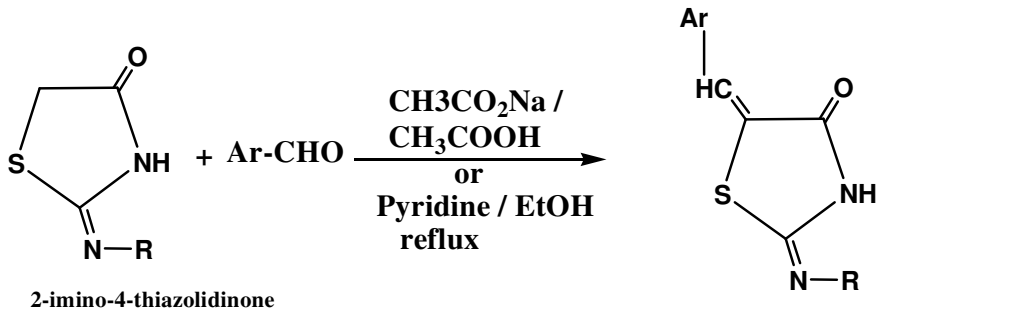


2-imino-4-thiazolidinone

2-imino-3-aminoalkyl /aryl- 4-thiazolidinone

Condensation reaction with aldehydes

The CH_2 group at fifth position of thiazolidin-4-one ring due to its acidity it undergoes condensation reaction with aldehydes or ketones in knoevenagel reaction[32]. In this reaction, formation of an enolate intermediate is stabilized, which is more dependent on the electron attractive effect of the C=O group adjacent to the CH_2 group and the presence of electron-attractive group at second position of thiazolidin-4-one ring[33]. The condensation reaction typically occurs in presence of glacial acetic acid and sodium acetate where sodium acetate functions as both alkali and as well as a dehydrating agent in piperidine solution or ethanol[34].



2-imino-4-thiazolidinone

2-imino-5-arylidene-4-thiazolidinone

ANTIDIABETIC ACTIVITY

4-Thiazolidinones are used mainly as anticoagulant and anti-thrombic agents in therapy. Over the past two decades, literatures related to the effects of thiazolidinones are used and their derivatives on diabetes and its complications are reported. The search for new thiazolidinones against diabetes and its complications, either isolated from traditional medicine or chemically synthesized, has been constantly expanding. The cellular and molecular mechanisms include protecting pancreatic beta cells from damage, improving abnormal insulin signaling, reducing oxidative stress/inflammation, activating AMP-activated protein kinase (AMPK), inhibiting α-amylase and α-glucosidases[34].

DIABETES MELLITUS

Diabetes Mellitus is a metabolic disorder characterized by the presence of chronic hyperglycemia accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids and proteins. Etiology of Diabetes Mellitus includes defect in either insulin secretion or response or in both at some point in the course of disease. Mostly patients with diabetes mellitus have either Type 1 diabetes (which is immune-mediated or idiopathic) Type 2 Diabetes Mellitus (formerly known as non-insulin dependent Diabetes Mellitus) are the most common forms of Diabetes Mellitus which is characterized by hyperglycemia, insulin resistance, and relative insulin deficiency[36].

Type 2 Diabetes Mellitus results from interaction between genetic, environmental, behavioural factors[37,38], and also includes gestational hormonal environment, genetic defects, other infections, and even due to certain drugs. The worldwide prevalence of diabetes has continued to increase dramatically. Globally, as of 2011, an estimated 366 million people had Diabetes Mellitus, with Type 2 making up about 90% of the cases[39,40]. The number of people with Type 2 Diabetes Mellitus is increasing in every country and 80% of the people living in low- and middle-income countries. The treatment goal of diabetic patients is to maintain near normal levels of glycemic control, in both fasting and post-prandial conditions.

Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. The percentage of deaths attributable to high blood glucose or diabetes that occurs prior to age 70 were higher in low- and middle-income countries than in high-income countries(WHO,2016). The maximum number of diabetic patients was recorded in India followed by china and USA. If the current condition prevails and nothing much is done in future, then by the year 2030, number of individuals affected by diabetes in India would raise up to 79 million.

CLASSIFICATION OF DIABETES MELLITUS

The classification of Diabetes Mellitus was based on etiological factors of the diseases. The old and confusing terms of insulin-dependent (IDDM) or non-insulin-dependent (NIDDM) which were proposed by WHO in1980 and 1985 have disappeared and the terms of new classification system identifies four types of diabetes mellitus: Type 1, Type 2, gestational diabetes and Monogenic diabetes.

TYPE 1 DIABETES MELLITUS

Type 1 diabetes mellitus (juvenile diabetes) is characterized by beta cell destruction caused by an autoimmune process, usually leading to absolute insulin deficiency. Type 1 is usually characterized by the presence of anti–glutamic acid decarboxylase and islet cell or insulin antibodies which identify the autoimmune processes that lead to beta cell destruction. Eventually, all Type1 diabetic patients will require insulin therapy to maintain normoglycemia.

TYPE 2 DIABETES MELLITUS

The relative defects in insulin secretion or in the exhibit intra-abdominal (visceral) obesity, which is closely related peripheral action of the hormone in the occurrence of Type 2 diabetes. This is the most common form of diabetes mellitus and is highly associated with family history of diabetes, older age, obesity and lack of exercise. Type 2 diabetes comprises 80% to 90% of all cases of Diabetes mellitus. Most individuals with Type 2 diabetes will be having insulin resistance, hypertension and dyslipidemia (high triglyceride and low HDL-cholesterol levels; postprandial hyperlipidemia) often present in the individuals. It is more common in women, especially women with a history of gestational diabetes, and in Blacks, Hispanics and Native Americans.

GESTATIONAL DIABETES MELLITUS (GDM)

Gestational diabetes mellitus is an operational classification (rather than a pathophysiologic condition) in which women who develop diabetes mellitus during gestation. Women who develop Type 1 diabetes mellitus during pregnancy and women

with undiagnosed asymptomatic Type 2 diabetes mellitus that is discovered during pregnancy are classified as Gestational Diabetes Mellitus (GDM). In most women who develop GDM; the disorder has its onset in the third trimester of pregnancy.

OTHER SPECIFIC TYPE (MONOGENIC DIABETES)

Types of diabetes mellitus of various known etiologies are grouped together to form the classifycation called "Other Specific Types". This group includes persons with genetic defects of beta-cell function (this type of diabetes was formerly called MODY or maturity-onset diabetes in youth) or with defects of insulin action; persons with diseases of the exocrine pancreas, such as pancreatitis or cystic fibrosis; persons with dysfunction associated with other endocrinopathies (e.g. acromegaly); and persons with pancreatic dysfunction caused by drugs, chemicals or infections and they comprise less than 10% of Diabetes Mellitus cases.

Importance of α-Amylase Enzyme in the Body

In humans, the digestion of starch involves several stages. Initially, partial digestion by saliva results in the degradation of polymeric substrates into shorter oligomers. Later on in the gut these are further hydrolyzed by pancreatic α-amylase into maltose, maltotriose and small malto-oligosaccharides. The digestive enzyme (α-amylase) is responsible for hydrolysing dietary starch (maltose), which breaks down into glucose prior to absorption. Inhibition of α-amylase can lead to reduction in post-prandial hyperglycemia in diabetic condition.

Importance of α-Glucosidase Enzyme in the Body

α-glucosidase is a membrane bound enzyme located on the epithelium of the small intestine, catalysing the cleavage of disaccharides to form glucose. Inhibitors can retard the uptake of dietary carbohydrates and suppress post-prandial hyperglycemia. Therefore, inhibition of α-glucosidase could be one of the most effective approaches to control diabetes. Glucosidases are not only essential to carbohydrates digestion, but also vital for the processing of glycoprotein and glycolipids. This enzyme is a target for antiviral agents that interfere with the formation of essential glycoproteins required in viral assembly, secretion and infection. Glucosidase are also involved in a variety of metabolic disorders and carcinogenesis[41,42].

ENZYMES[43]

Enzymes are proteins, macromolecules they catalyse the chemical reactions in biological systems. They are specific in nature.

There are three different types of enzymes in human body, they are.

1) Metabolic enzymes

They are the spark of life, the energy of life, and the vitality of life. In human body every biochemical reactions that occurs are catalyst and regulated by enzymes only and making them essential to cellular functions and health.

2) Food enzymes

By consumption of supplemental enzyme products and through the raw foods we eat these food enzymes get into the body. Raw foods are the source of digestive enzymes

when ingested. However raw food manifest only enough enzymes to digest the particular food, not enough to be stored in the body for the later use.

3) Digestive enzymes

Helps in digesting the food and the nutrients in the food are delivered to different parts of the body. The most important digestive enzymes are a) Proteases (split proteins into their monomers, the amino acids), b) Lipases (split fat into free acids and glycerol molecules), carbohydrates (split carbohydrates such as starch and sugar into sample sugars such as glucose) and d) Nucleases (split nucleic acid into nucleotides).In which α-amylase is one of the digestive enzyme since it begins its process by digesting the starch and breaks them into smaller pieces with two or three glucose units.

α – Amylase[44-45]

α- amylase is found in the saliva, pancreatic secretions, and in the gastrointestinal tract. It severs an obvious role in polysaccharide digestion. α-amylase determination has been recognized as an important role for the diagnosis of diabetes for many years because elevated levels of the enzyme are associated with liver and pancreatic disorders.

The structure of starch consists of glucose polymers linked by α-1,4 and α-1,6 glycosidic bonds. α-amylase is an enzyme that catalyses the hydrolysis of starch into sugar. Amylase hydrolyse internal α-1,4- glucosidic linkage in starch. Largely at random, to produce dextrins and disaccharides.

Strach (insoluble)

↓ **α**-amylase

Dextrins

↓ **α**-amylase

Disaccharides

↓ α – glucosidase

Monosaccharide glucose

↓

Readily absorbed in GIT

↓

Blood stream glucose level increases

First α-amylase degrade starch into dextrin's and then to maltose by hydrolyzing α-1,4 glucan bonds. In digestion, the primary role of α- amylase is to perform the first reaction of this process, generating dextrin's that are subsequently hydrolyzed by other enzymes. This will comes under the classification of carbohydrates.

Starch

Starch is the most important dietary source for humans. High content of starch is found in cereals, roots, tubers etc. Starch is a homopolymer composed of D- Glucose units held by α-glycosidic bonds. It is known as glucosan or glucan. Starch consists of two polysaccharide components – water soluble amylase and a water insoluble amylopectin. Chemically amylase is a long unbranched chain with 200- 1000 D-glucose units held by α-1,4- glycosidic linkages.

Amylopectin, on the other hand, is a branched chain with α-1,6 glucosidic linkages at the branching points and α-1,4 linkage in the other place. Amylopectin molecule, which is composed of a few thousand glucose units, looks like a branched tree with 20-30 glucose units/ branch.

Enzyme inhibitors [30]

The molecules which bind to enzymes and decrease their activity are termed as Enzyme inhibitors. Many drugs are enzyme inhibitors, since it can block an enzyme activity and correct a metabolic imbalance. Some of the enzyme inhibitors are also herbicides and pesticides. Not all molecules that bind to enzymes are inhibitors. There are also enzyme activators that bind to the enzyme it enhance the enzymatic activity, while enzymes substrates bind and are converted to products in the normal catalytic cycle of the enzyme.

The binding of an inhibitor can stop a substrate from entering the enzymes□s active site and/ or hinder the enzyme from catalysing its reaction. In the past the only way to discover these new inhibitors was by trial and error. This brute force approach is still successful and has even been extended by combinatorial chemistry approaches that

quickly produce large number of novel compounds and high- throughput screening technology to rapidly screen these huge chemical libraries for useful inhibitors.

α-Amylase Inhibitors[31]

The activity of α-amylase is reported to be inhibited incase of diabetes. Therefore these- amylase inhibitors are acting as anti-diabetic drugs that work by preventing the digestion of carbohydrates.

The inhibition of α- amylase is by,

Metal chelators, organic acids and heavy inorganic metal ions:

All metal chelators are strong inhibitors of amylase as they are metalloenzymes. Eg. EDTA, of the organic acids, citric acid and oxalic acid is found to be the most potent inhibitor of amylase. Heavy metal ions such as Al^{3+}, Fe^{2+}, and Hg^{2+} are known to inhibit amylase at higher concentration.

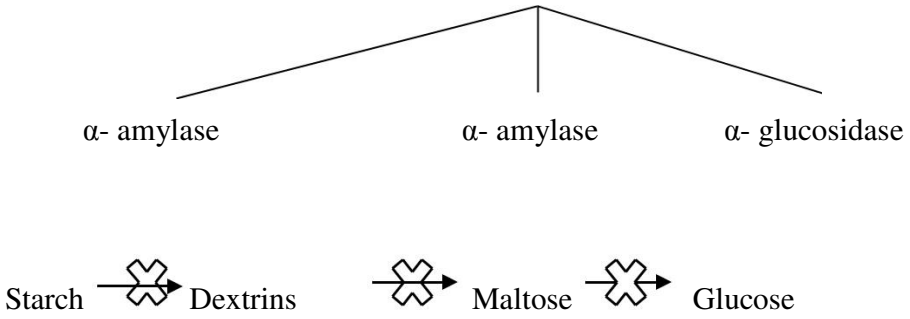
Crude plant extracts:

A number of crude plants extracts have been reported to have α- amylase inhibitory activity by many researchers. Some of the plant species like Murraya koenigii and Ocimum tenuiflorum extracts of which are reported to have appreciable α- amylase inhibitory activity.

Pure natural products:

A synthetic pseudotetrasaccharide, Acarbose originally isolated from microorganisms, is an established inhibitor of both α- amylase and α- glucosidase.

ACARBOSE



Pharmaceutical significance of α- amylase inhibitors:

α- amylase inhibitors inhibit the digestion and the production of glucose from complex polysaccharides. These inhibitors have the potential to supress post prandial blood glucose level in diabetic patients. Acarbose which lower blood glucose by inhibiting α- amylase and α- glucosidases is currently used as an antidiabetic drug.

Tendamistat (produced by stretomyces tendae and stretomyces lividans) is an extracellular polypeptide containing 74 amino acids, which showed significant biological activity similar to α- amylase inhibitor and it has been shown to have significant application in the treatment of diabetes mellitus. Due to its resistance against most hydrolytic enzymes, tendamistat would be orally available for the treatment of diabetes mellitus. Adiposin-1 (isolated from Streptomyces calvus) inhibits human α- amylase, is another example of potential antidiabetic compounds obtained from microbes.

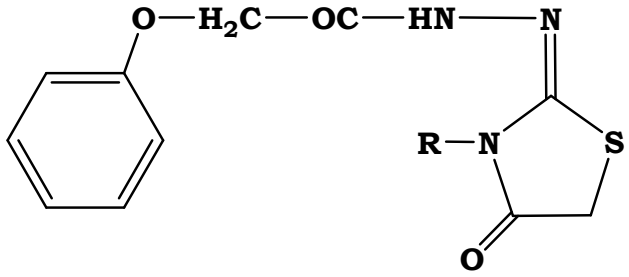
2. REVIEW OF LITERATURE

Various 4-thiazolidinone derivatives have been developed by structural modifications in order to enhance the biological properties such as anticonvulsant, anti-cancer, CNS depressant, analgesic, anti-inflammatory, etc. Herein a detailed literature survey is described for 4-thiazolidinone derivatives.

2.1. ANTIDIABETIC ACTIVITY

Pattan and co-workers[46] in the year 2005 reported the synthesis and anti-diabetic activity of 2-amino [5(-4–sulfonylbenzylidine)-2,4-thiazolidindione]-7-chloro–6 -flurobenzothiazole. The synthesized compounds were found to possess potent anti-diabetic activity.

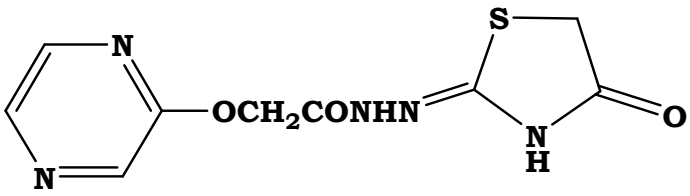
In the year 2009, Firake BM and co-workers[47] reported the synthesis of series of *N*-ary/alkyl substituted pyridine thiazolidinones **(1)**. These compounds were screened for their antidiabetic activity on wistar-strain rats and acute toxicity. All the tested compounds were found to possess good antidiabetic activity.



(1)

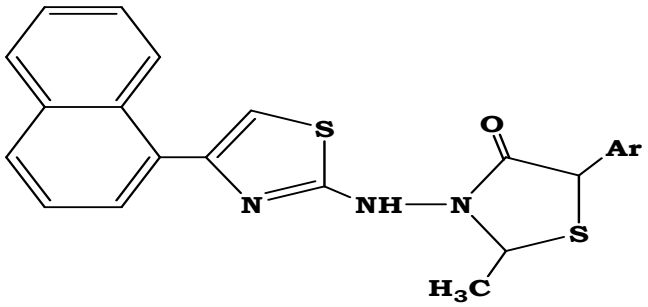
Suroor Ahmad Khan and co-workers[48] in the same year have prepared a series of 2-substituted phenyl-3-(1-naphthyl)-1,3-thiazolyl-amino-4-oxo thiazolidin acetic acid derivatives and evaluated their anti-hyperglycemic activity. The bioactivity results revealed that all compounds possess more potent antihyperglycemic activity.

In the year 2010, Vipan Kamboj and co-workers[49] synthesized a series of 3-(4-alkyl/arylsubstituted)-4-oxo-1,3-thiazolidin-2-ylidene acetohydrazide **(2)**. All the compounds were screened for their antidiabetic activity. Among the tested compounds, the compound 3-phenyl substituted-4–oxo-1,3-thiazolidin-2-ylidene acetohydrazide possess high activity with reduced toxicity.



(2)

Synthesis of 5-substituted-4-thiazolidinones **(3)** as anti-hyperglycemic activity was reported by Birendra Srivastava and co-workers[50] in the year 2010. These compounds were found to possess good anti-hyperglycemic activity.

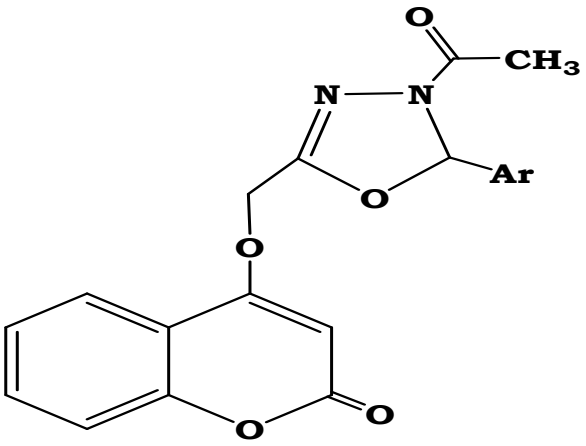


(3)

Deepthi Kini and co-workers[51] in the year 2011 reported the synthesis of new series of 3-(5-methyl-2-aryl-3-thiazolylamino)-4- thiazolidinone coumarin derivatives. The prepared compounds have been evaluated for their oral hypoglycemic activity. Among the tested compounds, the compound 3-(5-methyl-3-(4-nitrophenyl)-3-thiazolylamino-4-thiazolidinone coumarin exhibited high profile of activity when compared to standard.

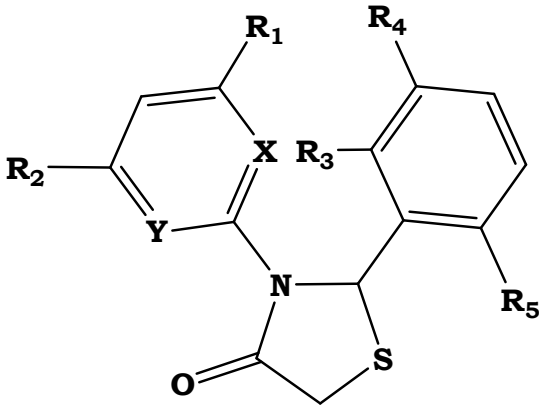
2.3. ANTI-VIRAL ACTIVITY

FaridBadria and co-workers[52] in the year 2003 synthesized a new thiazolidinone and oxadiazoline coumarin **(4)** derivatives and investigated their antiviral activity, cytotoxicity and SAR studies. All compounds were found to exhibits high antiviral profiles.



(4)

Synthesis of benzimidazole and thiazolidinone derivative **(5)** as HIV-1 RT inhibitors by microwave irradiation technique was reported by Anna Maria Monforte*et al.,*[53] in the year 2004. Among the evaluated compounds the compound 2-(2,6-difluorophenyl)-3-(3-methoxyphenyl)-1,3-thiazolidin-4-one emerged as potent HIV-1 with marked RT inhibitory affects.

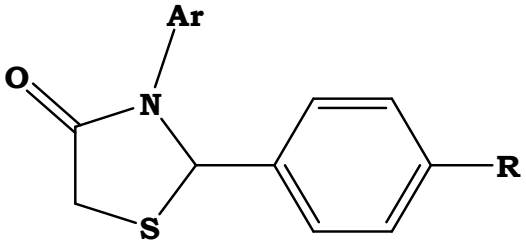


(5)

Zappala and co-workers[54] in the year 2004 synthesized 1,3-thiazolidinones with dihalogen and pyrimidine substitution. The prepared compounds were screened for their HIV-1 reverse transcriptase enzyme inhibition studies. From the activity data it was found that all the compounds were found to possess good HIV-1 activity.

In the year 2005, DharmarajanSriram and co-workers[55] reported the synthesis and anti-YFV activity of 2, 3-diaryl-1,3-thiazolidin-4-ones **(6)** by microwave-assisted reaction. The synthesized compounds were evaluated for their inhibitory effects on the

replication of YFV in green monkey kidney (Vero) cells (ATCC CCL81), by means of a cytopathic effect reduction assay.



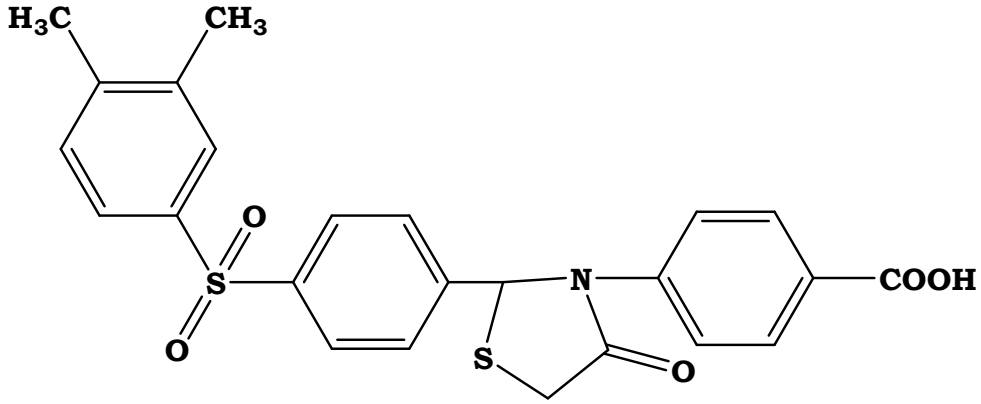
(6)

Ravindra K Rawal and coworker[56] in the year 2007 reported molecular docking studies of 4-thiazolidinones as HIV-1 RT inhibitors. The docking studies provided an insight into the pharmacophoric structural requirements for the HIV-1 RT inhibitory activity of this class of molecules.

In the year 2011, RavichandranVeerasamy and co-workers[57] has reported the design, synthesis and biological evaluation of thiazolidinone derivatives as potent anti-viral agents. All the compounds possessed high degree of antiviral potential.

2.4. ANTIMYCOBACTERIAL AND ANTIFUNGAL ACTIVITY

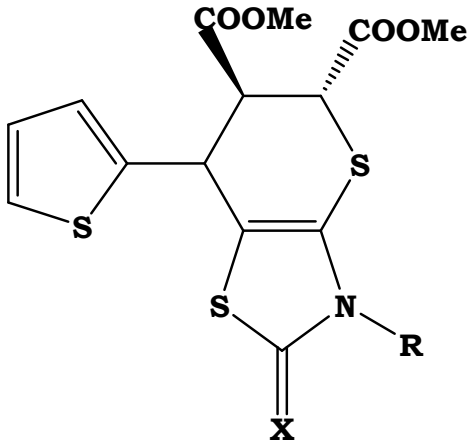
EvelinBoshra and co-workers[58] in the year 1989 reported some new heterocyclic thiazolidines **(7)** with acaricidal, insecticidal and bactericidal activity. The reported compounds were found to possess cgood bactericidal and inseticidal activities.



(7)

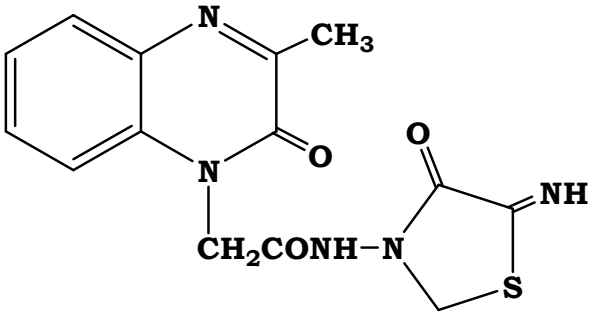
In the year 1990, HamedEad and co-workers[59] reported a cycloaddition reaction of series of 5-(2-thienyl) methylene **(8)** derivatives of thiazolidinone-4-thiones. The

synthesized compounds were screened for antimicrobial activities. The results of biological activity expressed that all compounds were more potent in nature.



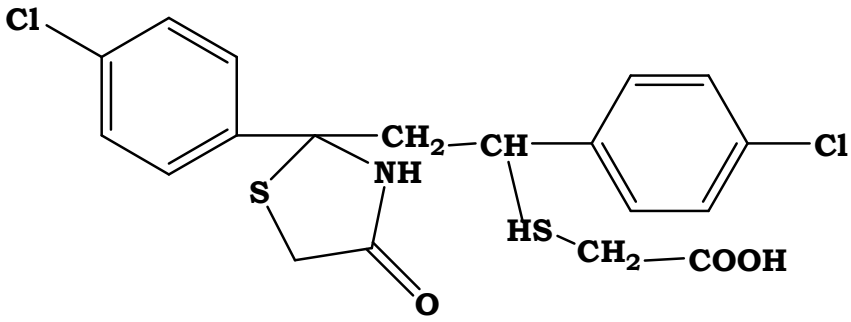
(8)

Preparation of quinoxaline derivatives containing thiazolidinone **(9)** residue as a potent antibacteial and antifungal agent was reported by Afaf K Ansary and co-workers[60] in the year 1995. All the compounds were found to exhibit significant antimicrobial activity.



(9)

Sayed R and co-workers[61] in the year 1999 synthesized a novel compound 2-[2-carboxymethylthio-2-(4-chlorophenyl) ethyl]-2-(4-chlorophenyl)-4-thiazolidinone **(10)** and studied its biological potency.

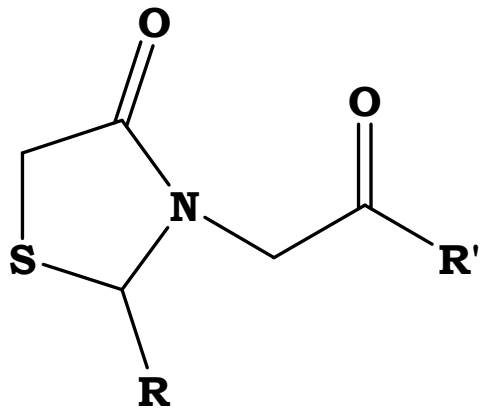


(10)

ANTICANCER ACTIVITY

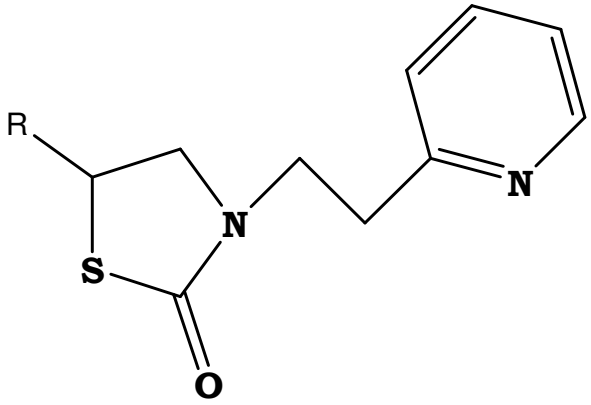
Monforte and co-workers[62] in the year 1988 reported the antitumor activity of series of 2-alkyl-[2-(1, 3, 4-thiadiazolyl)]-4-thiazolidinones. These compounds were tested against the leukemic 388 tumor system. All the compounds were found to exhibited significant antitumor activity.

Duane D Miller and co-workers[63] in the year 2004 reported the synthesis, SAR and antiproliferative activity of 2-aryl-4-oxo-thiazolidin-3-yl-amides **(11)** for prostate cancer. From this study, three potent compounds have been detected, which were effective in killing prostate cancer cells with improved selectivity.



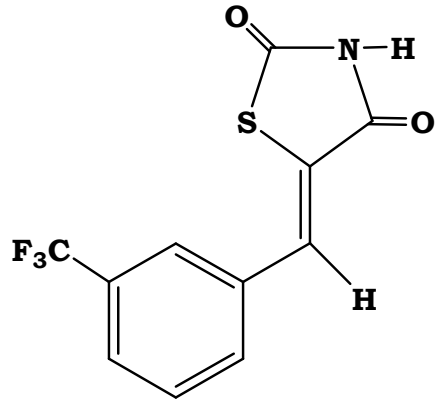
(11)

Roman Lesyk and co-workers[64] in the same year have reported some novel 4-thiazolidones **(12)** derivatives and studied their anti-diabetic (insulin-sensitizing), aldose reductase, thyromimetic, antimicrobial, antiviral, anti-ischemic, cardiovascular and anticancer activity.



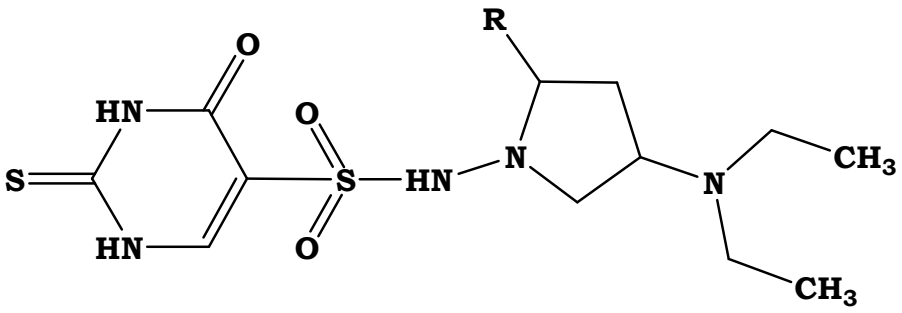
(12)

In the year 2005, StefaniaCarotti and co-workers[65] reported *in-vitro* anti-proliferative activity of 4-thiazolidinones against human colon cancer cell lines. The 2-phenylimino and 2,4-thiazolidinone **(13)** derivatives were found to be the most active compounds. 2-Phenylimino derivative inhibits the HT 29 cell line by a high COX-2 expression and 2,4-thiazolidinones inhibits all cell lines.



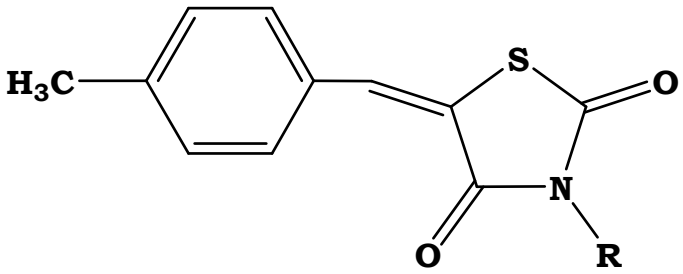
(13)

Amany Sayed Maghraby and co-workers[66] in the year 2005 reported the synthesis of series of new 4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine (1**4)** derivatives incorporated thiazolidinone moiety. The synthesized compounds were tested for possible serine prostate and cercarialelastase inhibitory effects with a possible prospective to block penetration of schistosomamansonicercariae in to the skin.



(14)

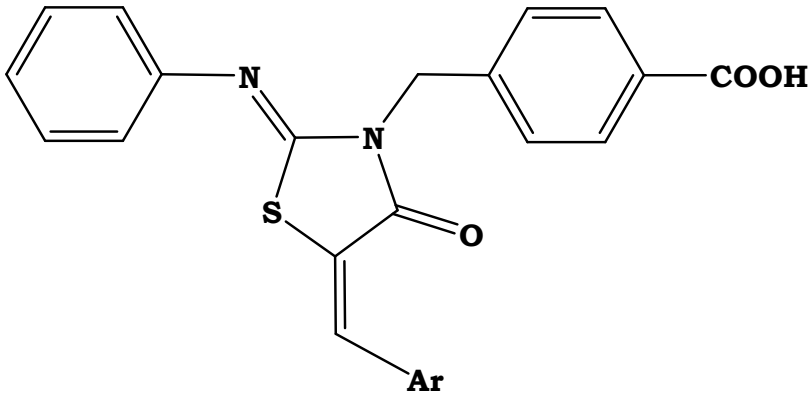
Benaka Prasad and co-workers[67] in the year 2008 synthesized a series of novel 5-(4-methyl benzylidene)-thiazolidine-2,4-dione **(15)** derivatives with different substituted aromatic sulfonyl chlorides and alkyl halides. The synthesized compounds were evaluated for their cell antiproliferative activity by MTT assay. The nitro group in the 4th position on aryl ring plays a dominant role and was responsible for the antiproliferative activity.



(15)

Shuhong Wu and co-workers[68] in the year 2008 reported the synthesis of pharmacophore of thiazolidinone derivatives. The synthesized compounds were evaluated for their structure activity relationship, cytoselective toxicity and anti-cancer activity.

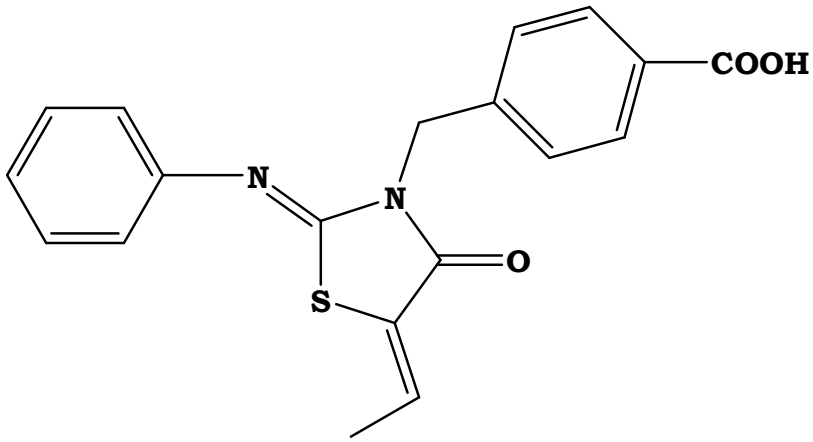
In the year 2009 Rosanna Maccari and co-workers[69] synthesized 4-(5-arylidene-4-oxo-2-phenylimino thiazolidin-3yl)-methyl benzoic acids **(16)** and screened their inhibitory activity against human PTP1b and LMW-PTP enzymes. Among the evaluated compounds, the 5-arylidene substituted moiety proved the potency.



(16)

In the same year, Zimenkovsky and co-workers[70] have synthesized a novel nonfused bicyclic thiazolidinones. These compounds were screened for their anticancer activity. Among the tested compounds, the compound 2-(4-oxo-3-furyl methyl-4-oxothiazolidin-5-yl-*N*-4-chlorophenyl) acetamide was found to be more potent anticancer agent than the standard compound.

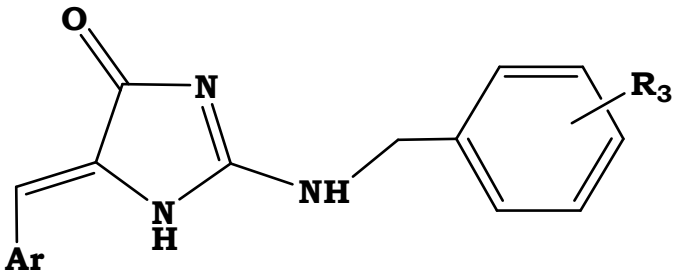
Havrylyuk Dmytro and co-workers[71] in the year 2010 reported the synthesis and anticancer activity evaluation of 4-thiazolidinones **(17)** containing benzothiazole moiety. These compounds were screened for *in-vitro* anticancer activity. The activity data exhibits that all compounds were found to show potent anticancer activity.



(17)

Kaminskyy DV and co-workers[72] in the year 2010 described the structure–anticancer activity relationships among 4-thiazolidinone-3-carboxylic acids derivatives.

In the year 2010, IvannaSubtelna and co-workers[73] synthesized the 5-arylidene-2-amino-4-thiazolones **(18)** and evaluated their anticancer activity. The synthesized compounds were found to possess a good anticancer activity. Among the tested one, the compounds 5-(4-chlorobenzylidene)-2-(4- hydroxyl phenyl amino) thiazol-4-one and 5-(2-chloro-3-(4-nitrophenyl)-2-propenylidene)-2-(3-hydroxyphenylamino) thiazol-4-one were found to possess high effect on all leukemia cell lines.



(18)

In the year 2011 Maity TK and co-workers[74] reported the synthesis, characterization and antiproliferative activity of 2-(substituted phenyl)-5-methyl-3-pyridin-4yl-1,3-thiazolidinones. These compounds were evaluated for *in-vitro* cytotoxicity against lymphoma cancer cell lines at varies concentrations. Among the tested compounds, two compounds showed highest cytotoxic activity against L929 cell lines.

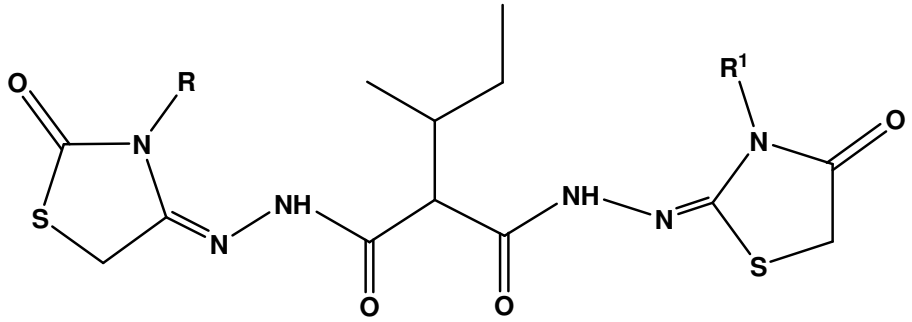
A series of regioselective 3-thiazolidine acetic acid derivatives were synthesized by Zhengming Li and co-workers[75] in the year 2011. These compounds were evaluated for anti-tumor activity. The results of bioactivity data showed that modification at the C-H of amino acid, N-(per-*o*-acetyl glycosyl amino) thioxo methyl) ethyl ester results in great influence on anti-tumor activity.

Ping Gong and co-workers[76] in the year 2012 reported the design and synthesis of 2-iminothiazolidin-4-one moiety-containing compounds as potent antiproliferative agents. The Pharmacological data indicated that most of the compounds possessed moderate activity, some showed remarkable activity.

2.5. ANTICONVULSANT ACTIVITY

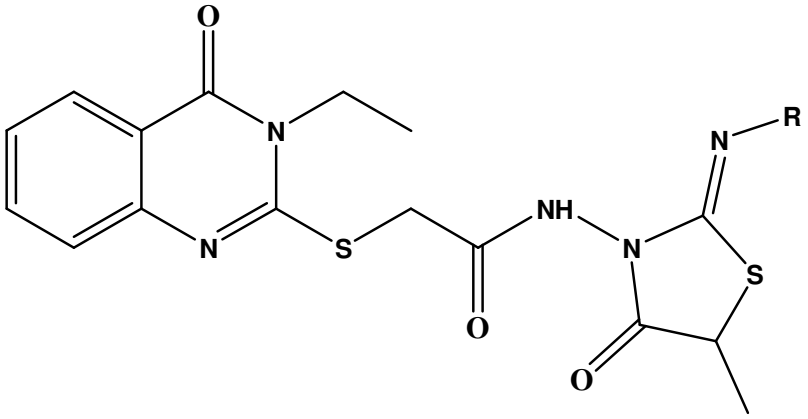
In the year 1996, Ulusoy and co-workers[77] have reported the synthesis, characterization and anticonvulsant evaluation of bis-thiazolidin-4-one **(19)**. The results

of biological activity indicate that substitution of phenyl group at 3rd position and alkyl group at 4th position results in potent activity.



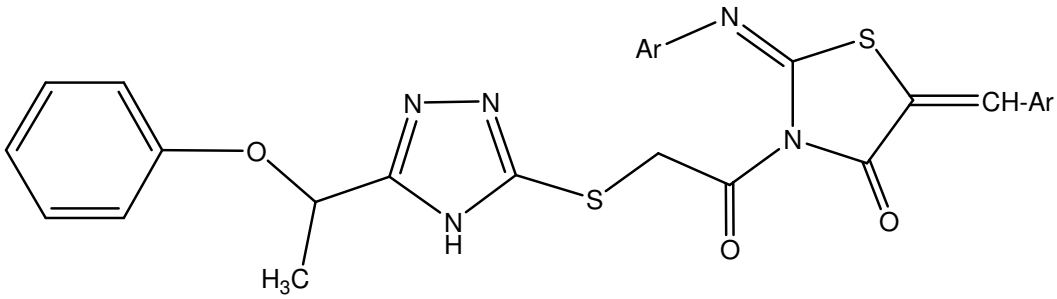
(19)

Aysel and co-workers[78] in 2005 have synthesized and isolated a new series of 2,3-regioisomeric substituted-4-thiazolidinones **(20)**. These compounds were screened for their anticonvulsant activity. The anticonvulsant data showed that substitution at 3rd position favors pronounced activity. These compounds were found to possess good anticonvulsant activity.



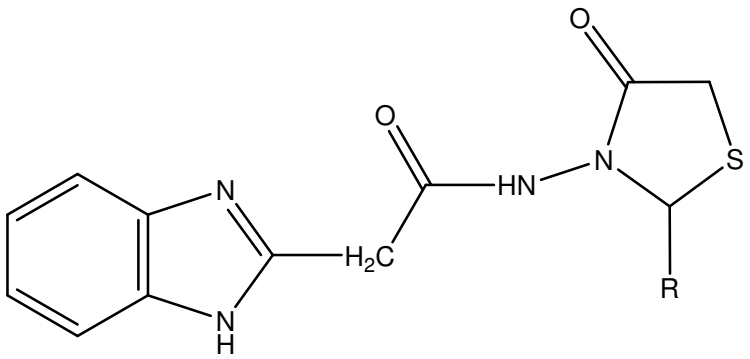
(20)

Kailash and co-workers[79] in the year 2007 reported the new series of triazole substituted thiazolidinone derivatives **(21)**. These compounds were evaluated for their neurotoxicity and anticonvulsant activity in two animal models of seizures. The results of screening data shown that, three compounds exhibited excellent anticonvulsant activity.



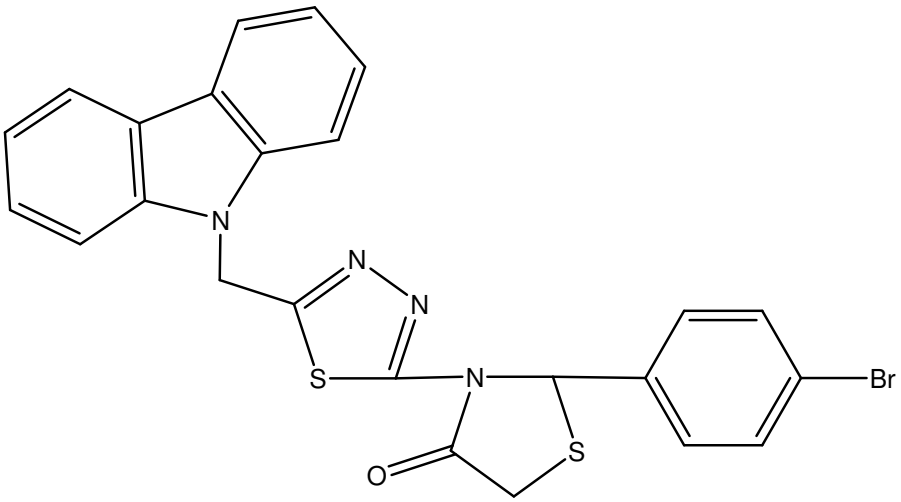
(21)

Huger and coworkes[80] in the year 2010 have synthesized a group of thiazolidinones containing 2-mercapto benzimidazole moiety **(22)** and screened them for *in-vivo*anticonvulsant activity by maximal electroshock (MES) model. The activity data reveals that all the synthesized compounds were found to possess potent anticonvulsant activity.



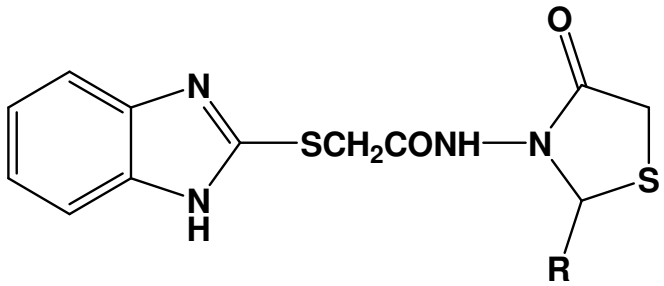
(22)

In the same year synthesis and anticonvulsant activity of novel substituted thiadiazolylazetidinonyl derivatives **(23)** were reported by Saxena and co-workers[81]. The activity data concludes that among the synthesized compounds, some of the title compounds exhibited promising anticonvulsant activity.



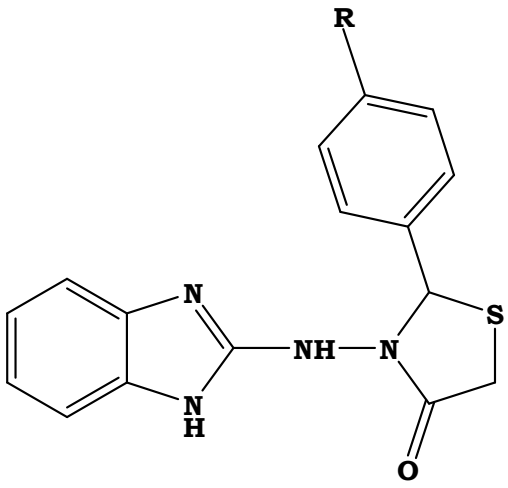
(23)

Rangappa and co-workers[82] in the same year reported synthesis of group of thiazolidin-4-ones and 1,3,4-oxadiazoles containing mercapto benzimidazoles **(24)**. The synthesized compounds were screened for *in-vivo* anticonvulsant activity by MES model and antidiabetic activity. All the compounds were exhibited potent anticonvulsant and antidiabetic activities.



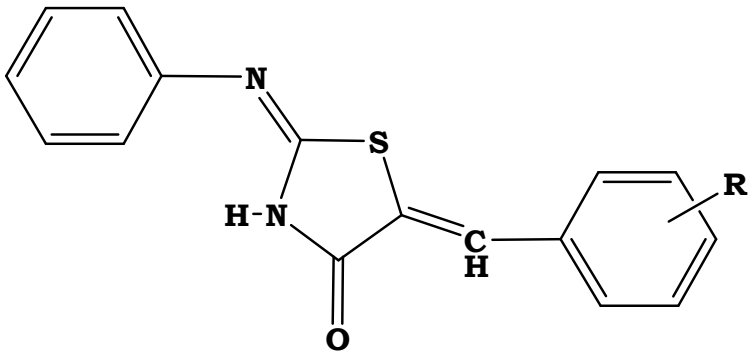
(24)

In the year 2011, Ganesh Akula and co-workers[83] prepared a series of benzimidazolyl amino thiazolidin-4-ones **(25)**. These compounds were screened for anticonvulsant activity by the MES induced seizure model. All the compounds were significantly showed their anticonvulsant activity similar to that of standard.



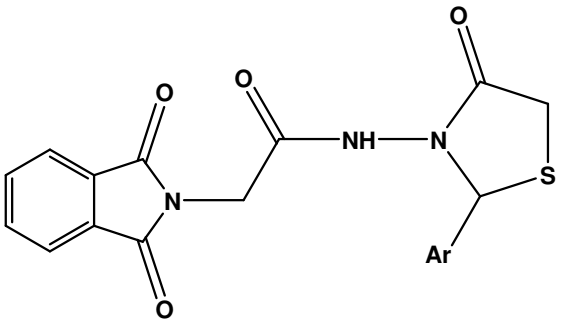
(25)

Tejprakash and co-workers[84] in the same year have synthesized and characterized a series of substituted 5-ethylidene-2-phenylimino-4-thiazolidinones **(26)**. These compounds were screened for their anticonvulsant activity. From the results they concluded that substitution in 5th position with electrophilic groups such as nitro group shows good anticonvulsant activity than the nucloephilic groups such as methoxy and methyl group.



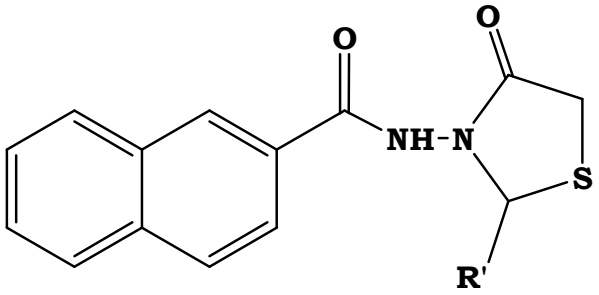
26)

Nikalje and co-workers[85] in the same year reported a series of 2-dioxoisoindolin-N-4-oxo substituted thiazolidinylacetamide derivatives **(27)**. All the compounds were evaluated for anticonvulsant and CNS depressant activity in mice by MES and pentylenetetrazole induced seizure model and also screened their neurotoxicity. The results reveals that all the compounds were showed protection against MES test to inhibit seizure.



(27)

In the year 2012, Indulatha*et al.* [86] have reported the synthesis of novel *N*-4-oxo-2-aryl and heteroaryl substituted thiazolidin-3-yl-3-carboxamido-2*H*-chromen-2-ones **(28)** as potent anticonvulsant agents. The activity results indicated that all the compounds exhibited 63 percent protection which is an indicative of having ability to prevent seizure spread at the dose level of 100 mg/kg when compared to the standard drug.



(28)

3. RESEARCH ENVISAGED

AIM OF THE STUDY

Diabetes mellitus is a major endocrine disorder affecting nearly 10% of the population all over the world. It is characterized by hyperglycemia and disturbances of carbohydrate, protein and fat metabolisms, secondary to an absolute or relative lack of the hormone insulin. The number of people in the world with diabetes has increased dramatically over recent years. It is also predicted that by 2030, India, China and the United States will have the largest number of people with diabetes. Currently treatment of diabetes, in addition to insulin supplement includes many oral hypoglycemic agents along with appropriate diet and exercise. The treatment goal of diabetic patients is to maintain near normal levels of glycemic control, in both fasting and post-prandial conditions.

Postprandial hyperglycemia has been proposed as an independent risk factor for diabetes mellitus. Therefore, control of postprandial hyperglycemia is suggested to be important in the treatment of diabetes. One of the effective method to control diabetes is to inhibit the activity of α-amylase enzyme which is responsible for the breakdown of starch to more simple sugars(dextrin, maltotriose, maltose, and glucose). This is contributed by α-amylase inhibitors, which delays the glucose absorption rate thereby maintaining the serum blood glucose in hyperglycemic individuals. This study is focused to investigate the inhibitory potentials of the synthesized thiazolidinone derivatives on α-amylase, the key enzyme responsible for carbohydrate hydrolysis.

4-thiazolidinone possess a wide spectrum of biological and pharmacological activity due to the presence of nitrogen and sulfur which is considered to be responsible for the structural features to impart their activities.

Despite an optimal use of available antidiabetic drugs (ADDs), many patients fail to experience therapeutic efficacy and others do so only at the expense of significant failure in reduction of elevated blood sugar level and toxic side effects. The limitations with the conventional ADDs highlighted the need for developing

newer antidiabetic agents with less toxic and more effective drugs are required. Thiazolidinones are five membered ring system containing sulphur and nitrogen atom, received a much attention of medicinal chemists due to their potential biological activities. Substituent's' at C-4 position of 4-thiazolidinone moiety results in potent α-amylase inhibitory activity. Prompted by these reports, we aimed to prepare the following series of novel 4-thiazolidinone derivatives as potent α-amylase inhibiting agents.

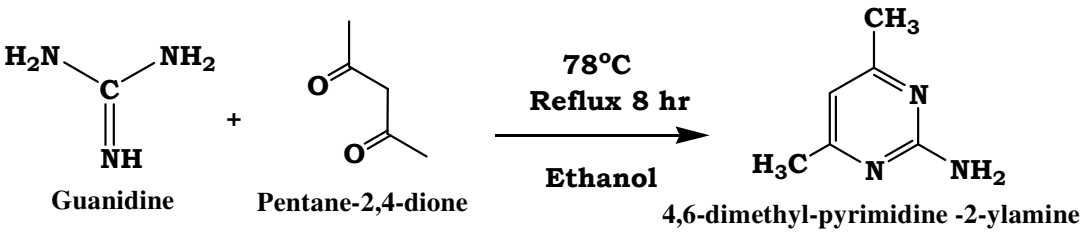
Hence the specific aims & objectives of the present study are

- To synthesize a series of novel 4- thiazolidinones.
- To characterize the synthesized compounds by IR, NMR, Mass spectra and elemental analysis.
- To evaluate the test compounds for its in vitro α-amylase inhibitory activity.
- The title compounds are planned to synthesize by using the following synthetic routes mentioned in the following schemes.

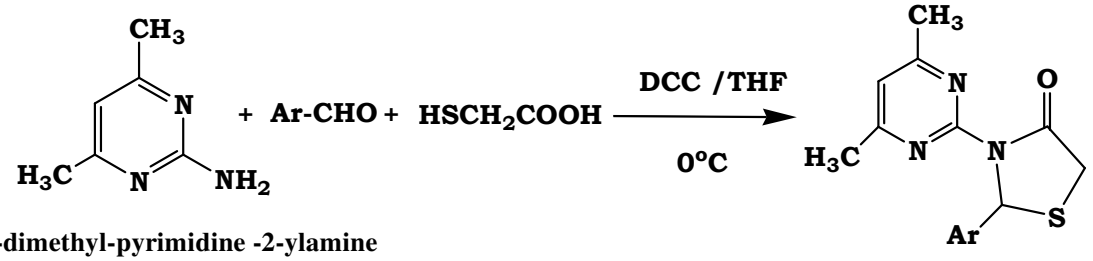
Scheme

Synthesis of 2-(4-substituted phenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one **(T1-T5).**

SCHEME

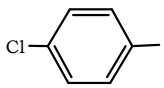


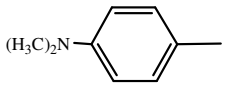
Guanidine **Pentane-2,4-dione** **4,6-dimethyl-pyrimidine -2-ylamine**

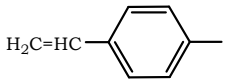


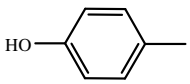
4,6-dimethyl-pyrimidine -2-ylamine

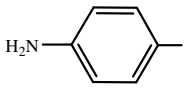
T1-T5

Ar = 1. 

2. 

3. 

4. 

5. 

CHAPTER–4

4.1. EXPERIMENTAL WORK

4.1.1 MATERIALS AND METHOD

Melting points (mp) were taken in open capillaries on thomas hoover melting point apparatus and are uncorrected. The IR spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 398 spectrometer. The ^{1}H spectra were recorded on a DPX-500 MHz Bruker FT-NMR spectrometer. The chemical shifts were reported as parts per million (δ ppm) tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). Elemental analysis was performed on a Perkin-Elmer 2400 C, H, N analyzer and values were within the acceptable limits of the calculated values. The progress of the reaction was monitored on readymade silica gel plates (Merck) using chloroform-methanol (9:1) as a solvent system. Iodine was used as a developing agent. Spectral data (IR, NMR and mass spectra) confirmed the structures of the synthesized compounds and the purity of these compounds was ascertained by microanalysis. Elemental (C, H, N) analysis indicated that the calculated and observed values were within the acceptable limits (± 0.4%). All chemicals and reagents were obtained from Aldrich (USA), or Spectro chem Pvt.Ltd (India) and were used without further purification.

4.1.1.1. General procedure for synthesis of 2-(4-substituted phenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T1-T5).

4-Thiazolidinones were synthesized in two steps. In the first step, 2-aminopyrimidine derivatives were synthesized by the reaction of 1,3-dicarbonyl compounds with guanidine. Final compounds (T1-T5) were synthesized by the reaction of compounds of step 1 with substituted aromatic aldehydes and mercaptoacetic acid, using DCC as intramolecular cyclizing agent (Figure 1).

Step-I: General procedure for the synthesis of 4,6-dimethyl-pyrimidin-2-ylamine.Equimolar solution of dicarbonyl compounds and guanidine in ethanol was refluxed at 78∘C for 8 hr. The reaction mixture was then concentrated to dryness under reduced pressure and the residue was partitioned in ethyl acetate. The organic layer was successively washed with water and then finally with ether. The organic layer was dried over sodium sulphate and the solvent was removed under reduced pressure to get 4,6-dimethyl-pyrimidin-2-ylamine[86]. The progress of the reaction was monitored by TLC, using methanol in chloroform (2:98) ratio.

Step-II: General procedure for the synthesis of compounds (**T1–T5**). A solution of 4,6-dimethyl-pyrimidin-2-ylamine (2 mol) and various substituted aldehydes (4 mol) was stirred in THF, under ice cold conditions for 5 min, followed by the addition of mercaptoacetic acid (3 mol). After 5 min, DCC (2 mol) was added to the reaction mixture at 0∘C and the reaction mixture stirred for an additional 5 hr at room temp and filtered. The filtrate was concentrated to dryness under reduced pressure and the residue was extracted with ethyl acetate. The organic layer was successively washed with 5% aqueous citric acid, water, and 5% aqueous sodium hydrogen carbonate and then finally with

brine. The organic layer was dried over sodium sulphate and the solvent was removed under reduced pressure to get the products[87] (**T1–T5**). The progress of the reaction was monitored by TLC, using the solvent system methanol: chloroform (2:98).

4.1.1.2. Synthesis of 2-(4-chlorophenyl)-3-(4, 6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T1)

Yield : 2.56 g; 77.0 % w/w

Melting Point : 216-218 °C

Rf Value : 0.86 (methanol: chloroform (2 :98).

Molecular Formula : $C_{15}H_{14}ClN_3OS$

Molecular Weight : 319.81(M+), 321(M+2)

IR (KBr) cm^{-1} : 3048 (Ar-CH), 2825 (CH_3),1710 (C=O),1597 (C=N Str), 688 (C-Cl).

^{1}H NMR ($CDCl_3$) δ ppm: 2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3),3.38 (s,1H,CH), 6.86 (d, *J = 8.0 Hz*, 1H, Ar-H), 7.00 (d, *J =8.0Hz*, 2H, Ar-H), 7.15 (d, *J =8.0Hz*, 2H, Ar-H).

Elemental Analysis

Calculated : C, 56.33; H, 4.41; N, 13.14.

Found : C, 56.31; H, 4.41; N, 13.12.

4.1.1.3. Synthesis of 2-(4- (dimethylamino) phenyl)- 3- (4,6-dimethylpyrimidin-2-yl) thiazolidin-4-one (T2).

Yield : 2.87 g; 83.4 % w/w

Melting Point : 245-247 °C

Rf Value : 0.79 (methanol: chloroform (2 :98).

Molecular Formula : $C_{17}H_{20}N_4OS$

Molecular Weight : 328.43(M+)

IR (KBr) cm^{-1} : 3085 (Ar-CH), 2948 (CH_3),1712 (C=O),1597 (C=NStr), 1289($N(CH_3)_2$, 1191 (C-S).

^1H NMR ($CDCl_3$) δ ppm: 2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3),2.85(6H, CH_3), 3.35 (s,1H,CH), 6.47 (s, *J = 8.0 Hz*, 2H, Ar-H), 6.88 (d, *J =8.0Hz*, 2H, Ar-H), 6.90 (s, *J =8.0Hz*, 1H, Ar-H).

Elemental Analysis

Calculated : C, 62.17; H, 6.14; N, 17.06

Found : C, 62.15; H, 6.13; N, 17.04

4.1.1.4. Synthesis of 3-(4,6-dimethylpyrimidin-2-yl)-2-(4-vinylphenyl)thiazolidin-4-one (T3)

Yield : 2.68 g; 77.6 % w/w

Melting Point : 238-240 °C

Rf Value : 0.72 (methanol: chloroform (2 :98).

Molecular Formula : $C_{17}H_{17}N_3OS$

Molecular Weight : 314.4(M+)

IR (KBr) cm^{-1} : 3058 (Ar-CH), 2852 (CH_3), 1698 (C=O),1628 (C=N Str), (1510) ($CH=CH_2$), 1191 (C-S).

^1H NMR ($CDCl_3$) δ ppm: 2.32 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.35(s,1H,CH), 5.62(s,2H, CH_2),5.92(s,1H,CH_2), 6.63(s,1H,CH),6.47 (s, *J = 8.0 Hz*, 2H, Ar-H), 6.86 (d, *J =8.0Hz*,1H,Ar-H), 7.00 – 7.18 (d, *J =8.0Hz*, 3H, Ar-H).

Elemental Analysis

Calculated : C, 65.57; H, 5.50; N, 13.49.

Found : C, 65.55; H, 5.50; N, 13.47.

4.1.1.5. Synthesis of 2-(4-hydroxyphenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T4).

Yield : 2.66 g; 80.7 % w/w

Melting Point : 264-266 °C

Rf Value : 0.78 (methanol: chloroform (2 :98)

Molecular Formula : $C_{15}H_{15}N_3O_2S$

Molecular Weight : 301.36(M+)

IR (KBr) cm^{-1} : 3532 (OH, broad), 3085 (Ar-CH), 2967 (CH_3), 1703 (C=O),1585 (C=N Str), 1191(C-S-C).

^1H NMR ($CDCl_3$) δ ppm:2.35 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.35(s,1H,CH),5.00(s,1H,OH),5.92(s,1H,CH_2), 6.61(s,2H,CH),6.86 (d,*J=8.0Hz*,1H,Ar-H), 6.81- 6.89 (d, *J =8.0Hz*, 3H, Ar-H).

Elemental Analysis

Calculated : C, 59.78; H, 5.02; N, 13.94.

Found : C, 59.76; H, 5.02; N, 13.92.

4.1.1.6. Synthesis of 2-(4-aminophenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T5)

Yield	:	2.93 g; 84.1.0 % w/w.
Melting Point	:	255-257 °C
Rf Value	:	0.81 (methanol: chloroform (2 :98)
Molecular Formula	:	$C_{15}H_{16}N_4OS$
Molecular Weight	:	300.38(M+)
IR (KBr) cm^{-1}	:	3383 (NH_2), 3076(Ar-CH), 2918 (CH_3), 1691(C=O), 1597 (C=NStr), 1191 (C-S).
^1H NMR ($CDCl_3$) δ ppm	:	2.32 (s, 3H,CH_3), 2.37(s,3H,CH_3), 3.33(s,1H,CH), 4.0 (s,1H,NH_2),5.92(s,1H,CH_2),6.34(s,2H,CH),6.86 (d,*J=8.0Hz*,1H,Ar- H),6.81-6.89 (d,*J =8.0Hz*, 3H, Ar-H).
Elemental Analysis		
Calculated	:	C, 59.98; H, 5.37; N, 18.65.
Found	:	C, 59.97; H, 5.37; N, 18.63.

4.2. CHROMATOGRAPHY STUDIES OF SYNTHESIZED COMPOUNDS

4.2.1 THIN LAYER CHROMATOGRAPHY

Thin Layer Chromatography or TLC is a solid-liquid form of chromatography here the stationary phase is a polar absorbent and the mobile phase can be a single solvent or Combination of solvents. TLC is in expensive technique and quick that can be used for determine the number of components in a mixture, verify a substance's identity, monitor the process of a reaction, determine appropriate condition for column chromatography, analyze the fractions obtained from column chromatography.

4.2.1.1 MATERIALS AND METHODS

1. Preparation of plates

Silicagel G was mixed in a glass mortar to smooth consistency with the requisite amount of water and slurry was quickly transferred to hespreader. The mixtures have been spread over the plates in thickness of 0.2mm and allow setting in to a suitable holder and after 30minutes; plates were dried at 120^{O}C, for further activation of the absorbent.

2. Sample application

About 2 mm of absorbent from the edge of plate was removed to gives sharply defined edges. 2-5µl volumes of synthesized compounds were spotted with the help of capillary tubes, just above1cm of the bottom of coated plates.

3. Development chamber

The chromatographic chamber was lined with filter paper dipping in to mobile phase so as to maintain the atmospheric saturation with solvent vapors in the chamber. The solvent front was allowed to rise to distance of about 12cm from the baseline on the plate was removed from the tank and allowed to dry in the air.

4. Solvent system

The choice of best developing solvent is one of the most important decisions in practical TLC by review of literature survey on by knowing nature of compounds, this solvent system used is (methanol: chloroform (2 :98).

5. Detection of components

The spots were visualized under iodine chamber.

4.2.2 COLUMN CHROMATOGRAPHY

Purification of synthesized compounds was done by column chromatography.

Materials

1. Glass column ofsize45 cm x3cm.

2. Silicagel for column chromatography 60-120 mesh size.

3. Eluting solvent system (methanol: chloroform (2 :98).

Preparation of column

The silica gel 60-120 mesh size was made in to slurry with the above solvent system. The bottom of the column was plugged with little glass wool. Then the slurry was poured in to the column, which is filled with solvent after two third of the column areas were filled with slurry. It was set aside for 30 minutes and eluting solvent was passed through column for several time ensure good packing of the column. After the adsorbents are settled, a filter paper was kept to prevent disturbance of the two player of the adsorbent as fresh mobile phase to be added to column for the process of elution. The fractions were collected for every 5m land analyzed for the presence of different of similar compound by running TLC and then allow evaporating to get the residue.

4.3. PHARMACOLOGICAL SCREENING

4.3.1. ENZYME INHIBITION STUDIES

DRUGS AND CHEMICALS

Acarbose (Bicon Ltd, Banglore), porcine pancreatic α-amylase (Sigma-Aldrich, USA), Glucose assay kits (Agappe Diagnostics, Kerala) 3, 5-dinitro salicyclic acid (HiMedia, Mumbai) and potato starch and maltose (Lobachemie,Mumbai) were purchased for the study. All the other chemicals used in the study were of analytical grade and were of commercial grade and obtained from respective manufacturers.

IN VITRO ANTIDIABETIC STUDIES

In vitro anti-diabetic potential of the synthesized thiazolidinone derivatives were studied by performing the enzyme inhibition assay using carbohydrate digestive enzymes i.e., α-amylase.

IN VITRO INHIBITION OF α- AMYLASE

The study was carried out with porcine pancreatic α-amylase with starch as substrate. Acarbose was selected as the standard drug for comparison of results and thiazolidinone derivatives dissolved in water.

PRINCIPLE[87]

α-amylase digests the starch in reaction mixture to yield maltose. The maltose produced would reduce the 3, 5-dinitrosalicyclic acid in the coloring agent to 3 amino 5-nitrosalicyclicacid. The reaction mixture produced a colour change from orange to red. The intensity of red colour will be directly proportional to the amount of maltose produced. When an enzyme inhibitor is present in reaction mixture digestion of starch, production of maltose and intensity of red colour produced will be less.

PREPARATION OF REAGENTS[88-89]

Preparation of Phosphate Buffer

Phosphate buffer (20 mM) of pH 6.9 (prepared with sodium phosphate monobasic and sodium chloride)

Preparation of Starch Solution

Starch solution (1.0%) prepared with phosphate buffer by boiling.

Preparation of Coloring Reagents

Colouring reagent is prepared by slowly adding sodium potassium tartarate solution [prepared in the ratio 12 g of solid dissolved in 8 ml of 2M sodium hydroxide] to 20 ml of 96 mM 3,5-dinitrosalicyclic acid (prepared in distilled water) and then diluting the mixture to 40 ml with distilled water.

Preparation of enzyme solution

Enzyme solution, alpha amylase (0.5 mg/ml) prepared with phosphate buffer pH 6.9.

PROCEDURE[90-92]

From 1 mg/ml stock solution different concentration (5-500 µg/ml) of 4-thiazolodinone derivatives were prepared by adding few drops of dimethyl sulfoxide and volume made up with water. About 500 µl of α-amylase (0.5 mg/ml) was added and was incubated for 10 minutes at room temperature. Then added 500µl of 1.0% starch solution and incubated for another 10 minutes. After that 1 ml of the coloring reagent was added to the reaction mixture and heated in a boiling water bath for 5 minutes. After cooling, 10 ml of distilled water was added for dilution. To measure the absorbance of the colored extracts, blank was prepared for each set of concentration of test sample by replacing the enzyme solution with buffer. Control incubations representing 100% enzyme activity was prepared

by replacing the test drug with water. The absorbance was then measured at 520 nm. The α-amylase inhibition was expressed as percentage of inhibition and the IC_{50} values determined by linear regression plots with varying concentration of synthesized thiazolidinone against percentage inhibition.

CALCULATION OF PERCENTAGE OF INHIBITION:

$$\text{PERCENTAGE INHIBITION} = \frac{C-T}{C} \times 100$$

Statistical Analysis

All values are expressed as mean ± SEM. Data were analyzed by non-parametric ANOVA followed by Dunnett's multiple comparison tests, and other data was evaluated using Graph Pad PRISM software. A *p*-value < 0.05 was considered significantly different.

CHAPTER– 5

RESULTS AND DISCUSSION

5.1. Chemical work:

The results of the present work are discussed under the following heads.

Scheme: 2-(4-substituted phenyl)-3-(4, 6-dimethylpyrimidin-2-yl) thiazolidin-4-one (**T1-T5**).

5.1.1. Synthesis of 2-(4-substituted phenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one.

Synthetic route depicted in scheme outline the chemistry part of the present work. 2-(4-substituted phenyl)-3-(4, 6-dimethylpyrimidin-2-yl)thiazolidin-4-one **(T1-T5)** were obtained by the condensation of dimethyl-pyrimidin-2-ylamine and various substituted aldehydes were stirred in THF, followed by the addition of mercaptoacetic acid and DCC. The formation of the substituted 4-thiazolidinones were confirmed by the presence of characteristic peaks in the IR spectra. It showed characteristic peaks at around 3400 cm^{-1} for NH_2 stretching and peak around 2900 cm^{-1} due to the presence of N=CH stretching. The NMR spectrum of the compounds (**T1-T5)** showed the characteristic peak around δ 2.70 ppm for CH_3 group, δ 3.00 ppm for CH_2 and δ 5.70 ppm for NCH and also shows multiplet in the range of δ 6.80-8.30 ppm owing to aromatic protons. The appearance of peak due to chlorine in IR spectra around 700 -800 cm^{-1} and formation M+2 peak in the mass spectra. Data from the elemental analyses and molecular ion recorded in the mass spectra further confirmed the assigned structure.

5.2. Pharmacological Investigation

Evaluation of α-amylase inhibitory activity

All the newly synthesized compounds were screened for *in vitro* α-amylase inhibitory activity at 5, 10, 25, 50, 100, 200, 400, 500μg/ml concentration. Acarbose was used as a standard drug in the same concentration. A graded increase in the percentage of inhibition was observed with increase in concentration.

The synthesized compounds in which IC_{50} of compound-T1 (25 μg/ml) and other 4 compounds in which IC_{50} of compounds-T_2 (35 μg/ml) and T_5(30μg/ml) showed percentage of inhibition closer to that of standard(Acarbose-12 μg/ml). The IC_{50} values of synthesized compounds were found by plotting a graph of percentage inhibition verus concentration in μg/ml. The values were compared with that of standard.

Among the synthesized compounds, T1 and T5 showed good percentage of inhibition at all concentration (5 μg/ml-500 μg). The IC50 values for these compounds were found to be 25 μg/ml and 30 μg/ml respectively which are close to IC50 value of acarbose (10 μg/ml). T3 and T4 showed moderate α-amylase inhibitory activity at all concentrations. The IC50 value for these compounds found to be 59 μg/ml and 110 μg/ml respectively.

T1 (*p*-chlorophenyl) produced IC50 value (25 μg/ml) which is relatively less value of IC50 indicates the sample has better α-amylase inhibitory activity which has significant α-amylase inhibitory activity when compared to that standard.

T2 (dimethylamino group) produced IC50 value (35 μg/ml) which is relatively less value of IC50 indicates the sample has more α-amylase inhibitory activity which has significant α-amylase inhibitory activity when compared to that standard.

T3 (dimethylamino cinnamaldehyde group) produced IC50 value (110 µg/ml) which is least value of IC50 indicates the sample has less α-amylase inhibitory activity when compared to that standard.

T4 (*p*-hydroxyl group) produced IC50 value (59 µg/ml) which is least value of IC50 indicates the sample has less α-amylase inhibitory activity when compared to that standard.

T5 (*p*-amino group) produced IC50 value (30 µg /ml) which is relatively less value of IC50 indicates the sample has more α-amylase inhibitory activity when compared to that standard.

The best mean IC50 values were achieved with compound (T1, T2, and T5) with slight difference among them.

Among the test compounds, compound **2-(4-chlorophenyl)-3-(4, 6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T1)** was found to be the most active agent which showed 88.00 µg/ml α-amylase inhibition in the highest concentration, which have *p*-chloro phenyl group in the 4-thiazolidinone nucleus.

PERCENTAGE OF α-AMYLASE INHIBITORY POTENTIAL OF SYNTHESISED COMPOUNDS
IN VITRO α-AMYLASE INHIBITORY ACTIVITY

Compound code	5 µg/ml	10 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	200 µg/ml	400 µg/ml	500 µg/ml	IC50 µg/ml
T1	33.75	41.25	54.50	60.41	65.00	75.00	85.00	88.00	25
T2	29.16	40.46	44.83	49.25	64.16	67.33	78.75	81.58	35
T3	19.16	28.83	42.79	42.75	49.85	58.75	73.58	79.00	110
T4	24.54	30.58	35.75	42.16	57.67	60.46	71.16	79.06	59
T5	30.69	35.47	46.81	56.25	68.75	77.50	80.16	85.40	30
Standard (Acarbose)	27.28	46.17	52.05	63.34	73.11	79.24	82.21	94.01	12

CHAPTER– 6

SUMMARY AND CONCLUSION

In summary, a new series of 2-(4-substituted phenyl)-3-(4, 6-dimethylpyrimidin-2-yl) thiazolidin-4-one (**T1-T5**).were synthesized. These title compounds containing five different substituent's at C-4 position were screened for their α-amylase inhibitory activity. Most of the test compounds were found to exhibit significant α-amylase inhibitory activity in the lowest concentration. Among the substituent's at C-4, *p*-chloro phenyl substituent shows maximum α-amylase enzyme inhibitory potency, while 4-aminophenyl and 4-dimethylaminophenyl substituent showed equipotent or has little less α-amylase inhibitory activity when compared to compound T1, but the dimethylamino cinnamldehyde and 4-hydroxy phenyl substituent exhibited least α-amylase inhibitory activity when compare to other substituents. The order of activity at C-4 is *p*-chloro phenyl ≥ p-amino phenyl ≥ p-dimethylaminophenyl ≥ 4- hydroxyl phenyl ≥ p-dimethylamino cinnamldehyde substituents.

Among the test compounds, compound **2-(4-chlorophenyl)-3-(4, 6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T1)** was found to be the most active agent which showed 88.00 µg/ml α-amylase inhibition in the highest concentration, which have *p*-chloro group in the thiazolidinone nucleus.

Hence this molecule can be selected as a lead molecule of the present study for further exploitation.

CHAPTER– 7

FUTURE PLAN OF WORK

It may conclude that further beneficial pharmacophore modifications in the design of novel 4-thiazolidinone derivatives may be synthesized by designing novel ligands for therapeutic target by substituting different functional group and also examine with the help of NMR and X-ray which provide three dimensional frame works which can analyze structure activity data and can guide the design and synthesis of future potential therapeutic drugs towards other chronic disorders.

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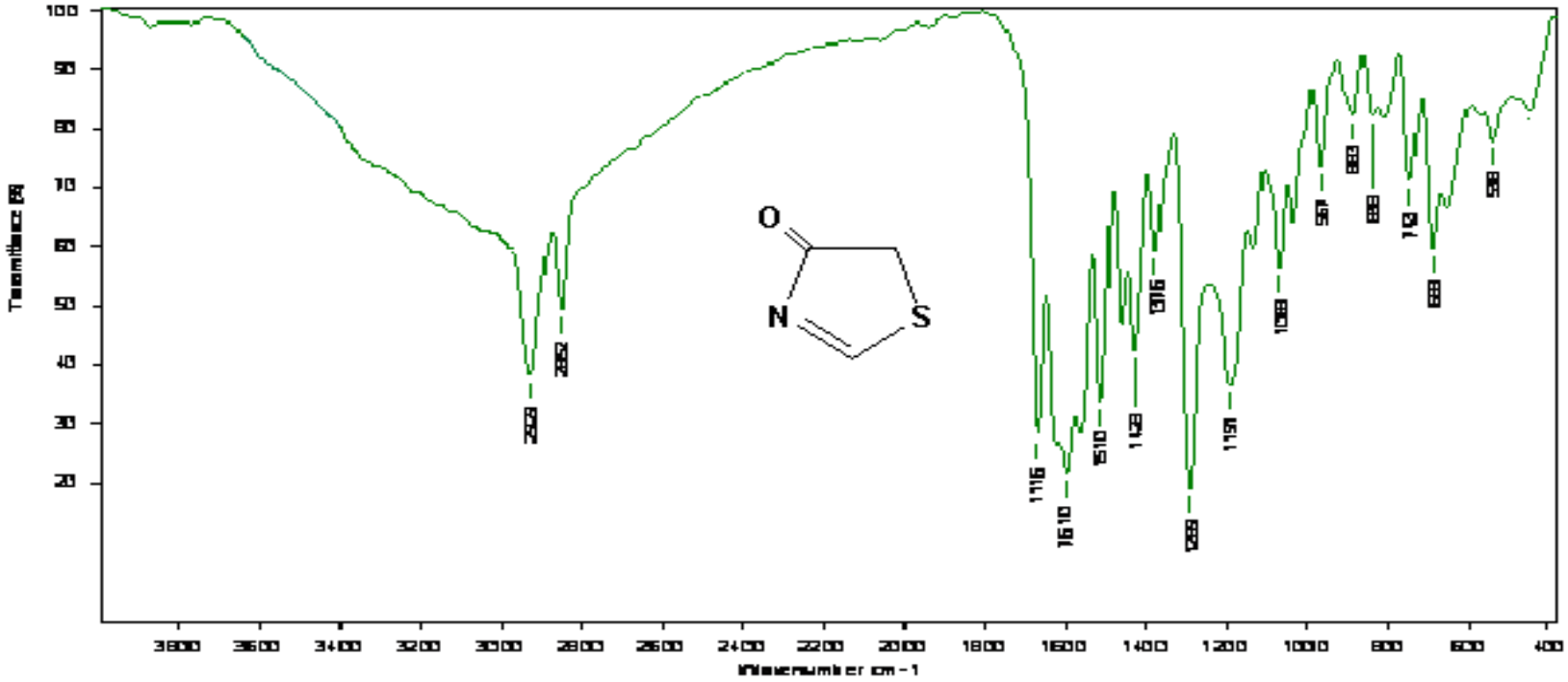
Compound Name: 4-Thiazolidinone



4-Thiazolidinone

Experiment: TRA 88.asm

Operator Name: Administrator

Instrument Type: Alpha

Sample Form: solid

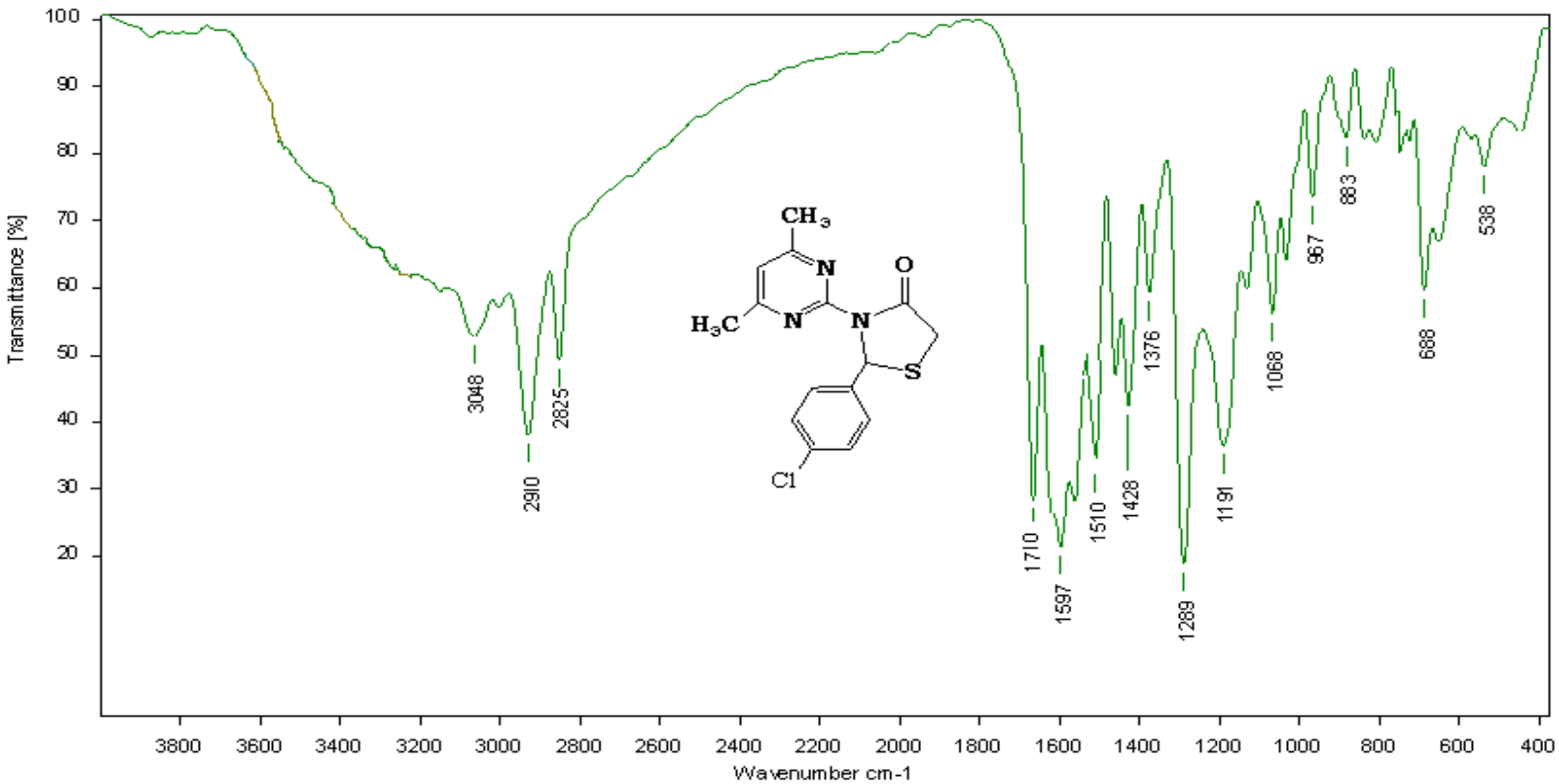
Sample Beams: 16

Analysis Name: sendhilraja

JKK Nataraja College of Pharmacy
Kumarapalayam

4/20/20183:20:26 PM

Compound Name: T1



2-(4-chlorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T1)

Experiment TRANS.xpm

Path of File C:\Program Files\OPUS_65\MEAS

Operator Name Administrator

Date of Measurement 20/04/2018

Instrument Type Alpha

Sample Form solid

Resolution 4

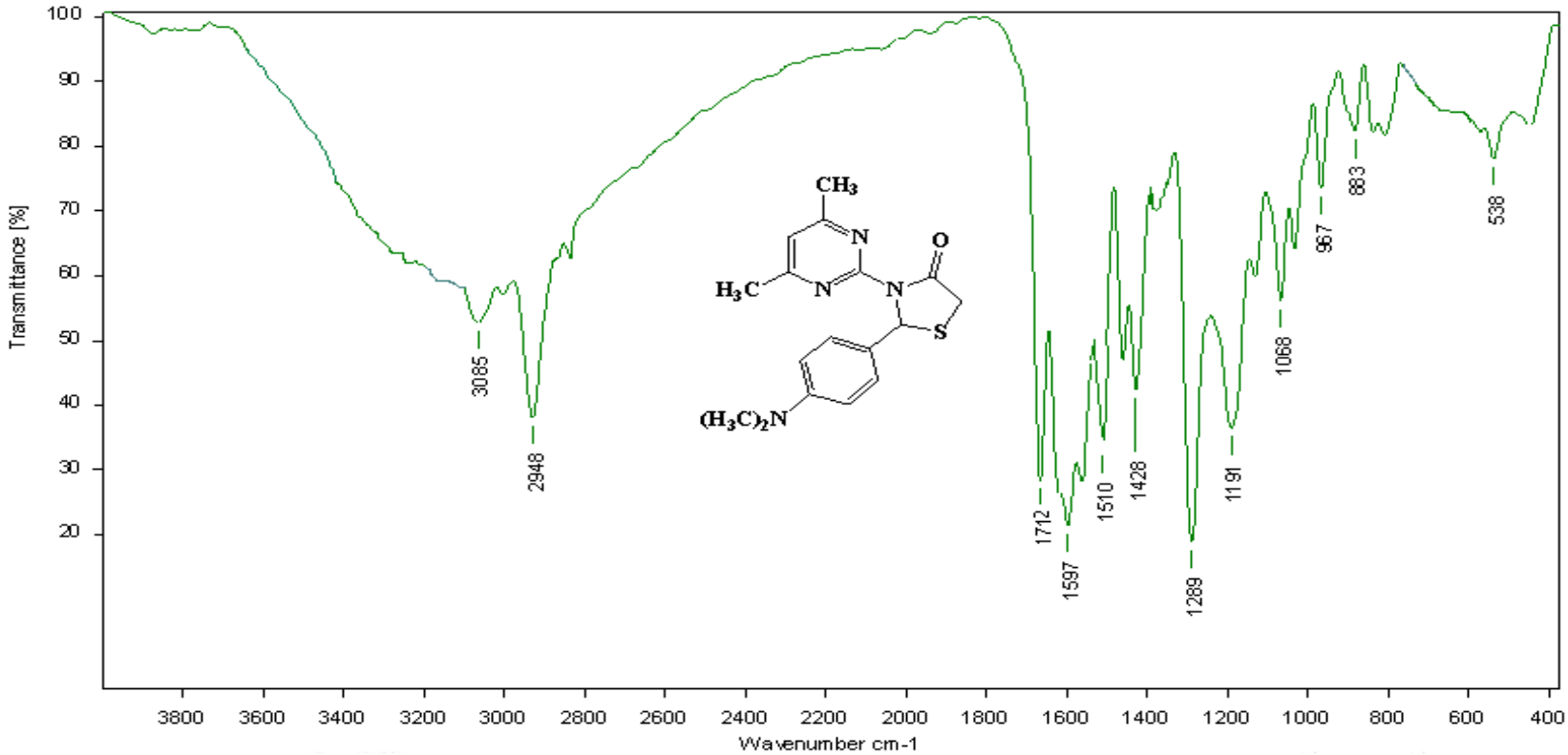
Sample Scans 16

Analyst name: senthilraja

JKK Nataraja College of Pharmacy
Kumarapalayam

4/21/2018 2:32: 50 PM

Compound Name: T2



2-(4- (dimethylamino) phenyl)- 3- (4,6-dimethylpyrimidin-2-yl) thiazolidin-4-one (T2).

Experiment TRANS.xpm

Operator Name Administrator

Instrument Type Alpha

Resolution 4

Analyst name: senthilraja

Path of File C:\Program Files\OPUS_65\MEAS

Date of Measurement 21/04/2018

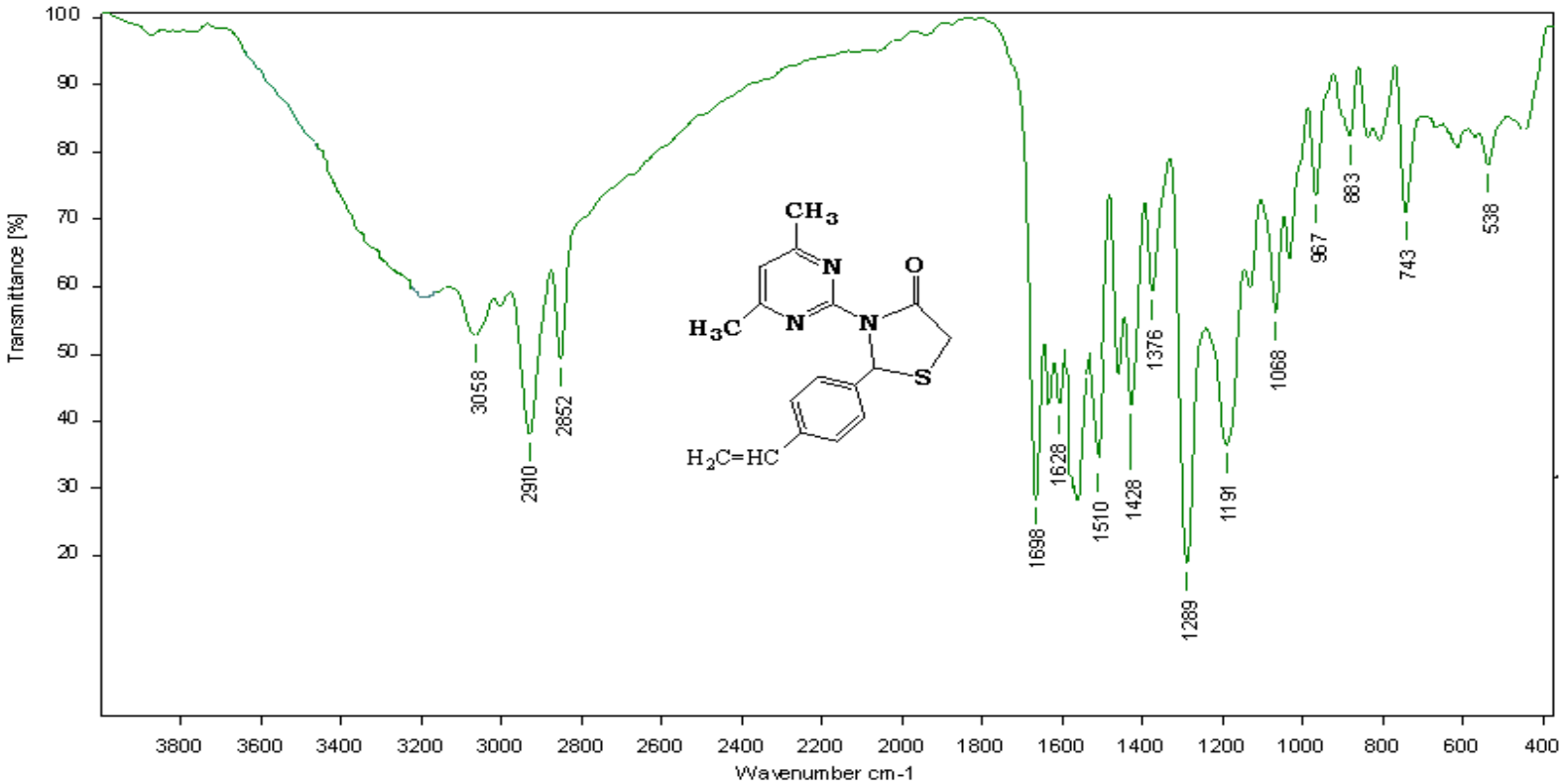
Sample Form solid

Sample Scans 16

JKK Nataraja College of Pharmacy
Kumarapalayam

4/21/2018 2:40:13 PM

Compound Name: T3



3-(4,6-dimethylpyrimidin-2-yl)-2-(4-vinylphenyl)thiazolidin-4-one (T3)

Experiment TRANS.xpm

Path of File C:\Program Files\OPUS_65\MEAS

Operator Name Administrator

Date of Measurement 21/04/2018

Instrument Type Alpha

Sample Form solid

Resolution 4

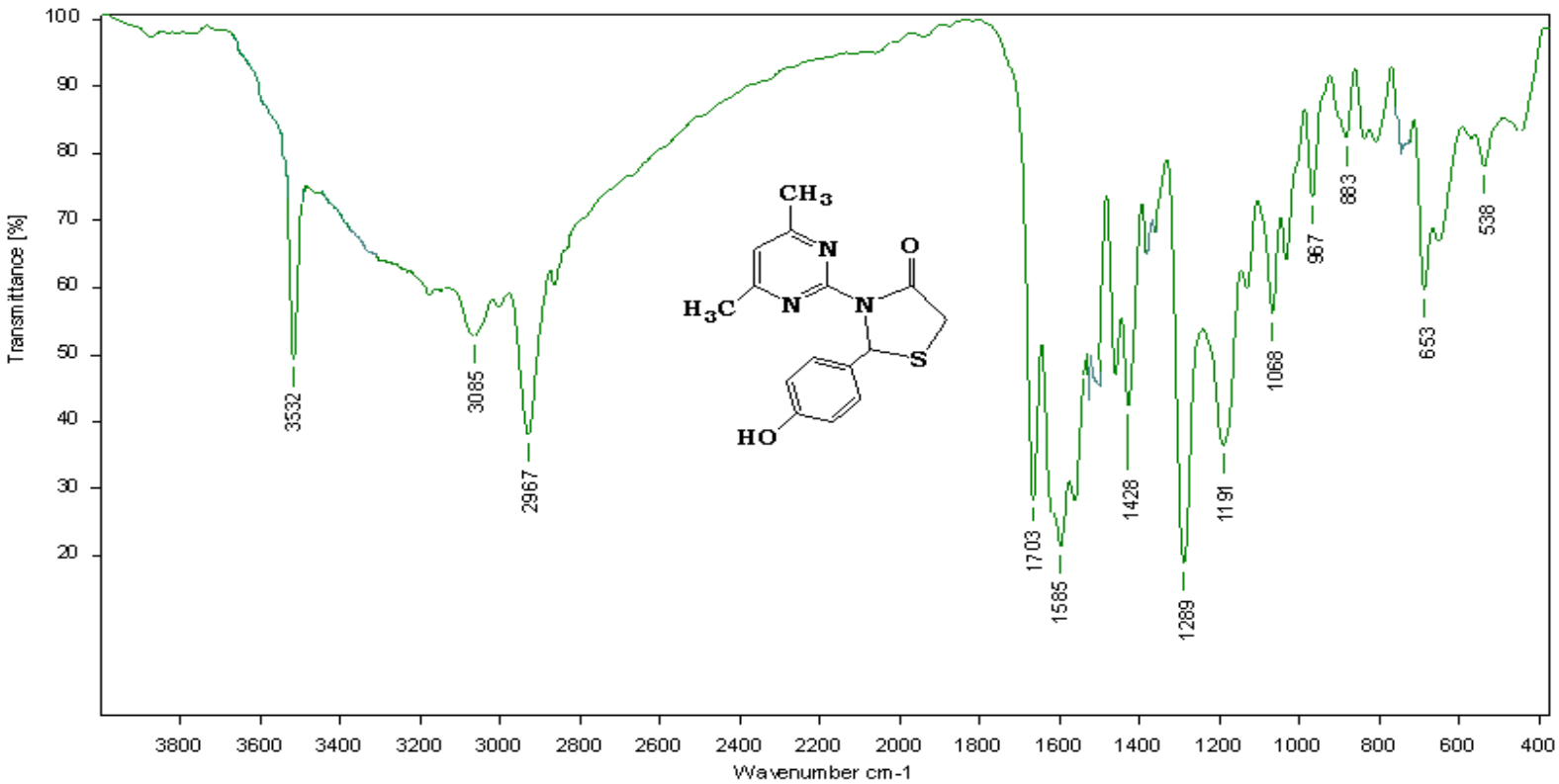
Sample Scans 16

Analyst name: senthilraja

JKK Nataraja College of Pharmacy
Kumarapalayam

4/23/2018 2:38:26 PM

Compound Name: T4



2-(4-hydroxyphenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T4).

Experiment TRANS.xpm

Path of File C:\Program Files\OPUS_65\MEAS

Operator Name Administrator

Date of Measurement 23/04/2018

Instrument Type Alpha

Sample Form solid

Resolution 4

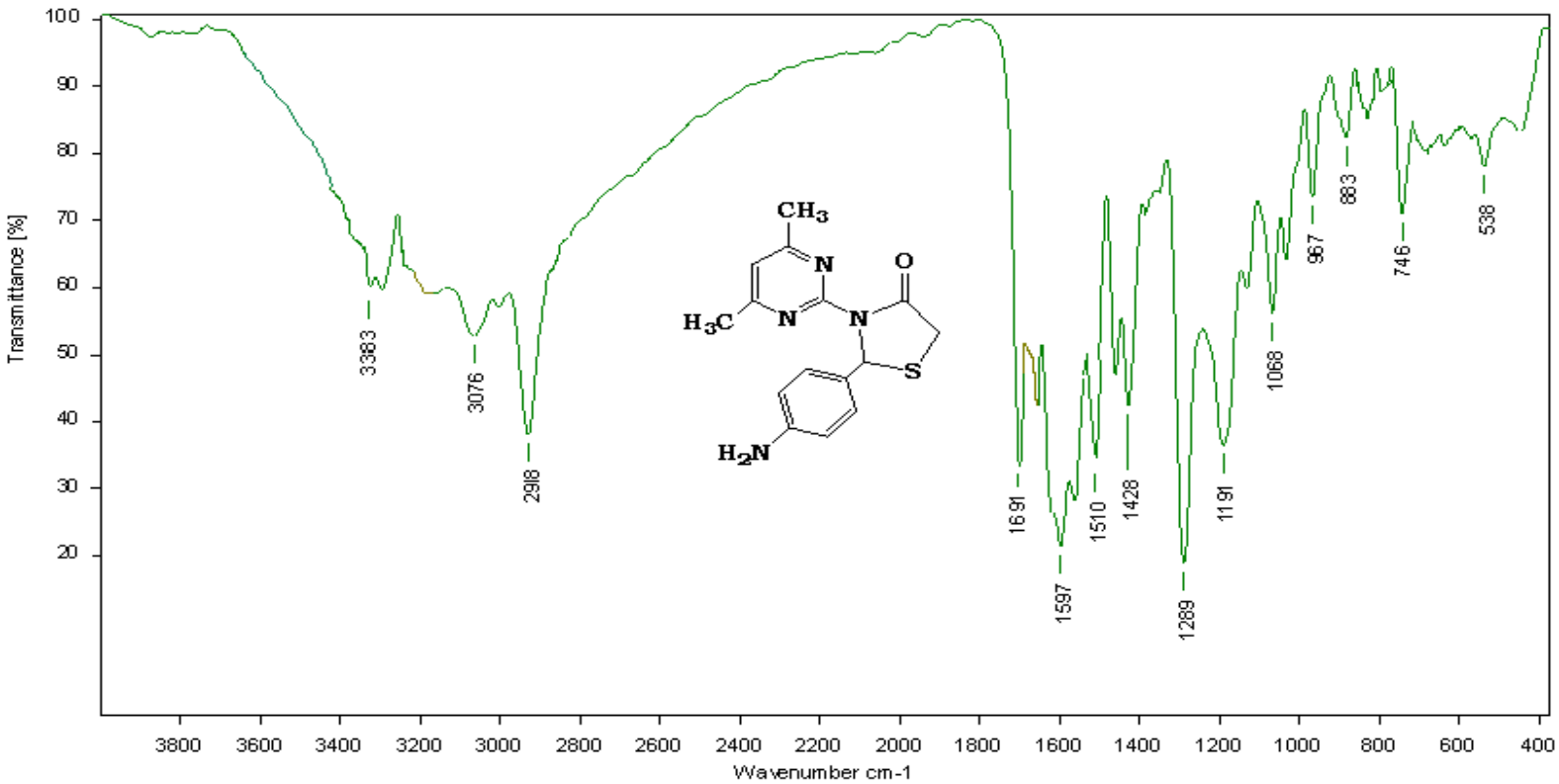
Sample Scans 16

Analyst name: senthilraja

JKK Nataraja College of Pharmacy
Kumarapalayam

6/23/2018 2:15:26 PM

Compound Name: T5



2-(4-aminophenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T5)

Experiment TRANS.xpm

Path of File C:\Program Files\OPUS_65\MEAS

Operator Name Administrator

Date of Measurement 23/06/2018

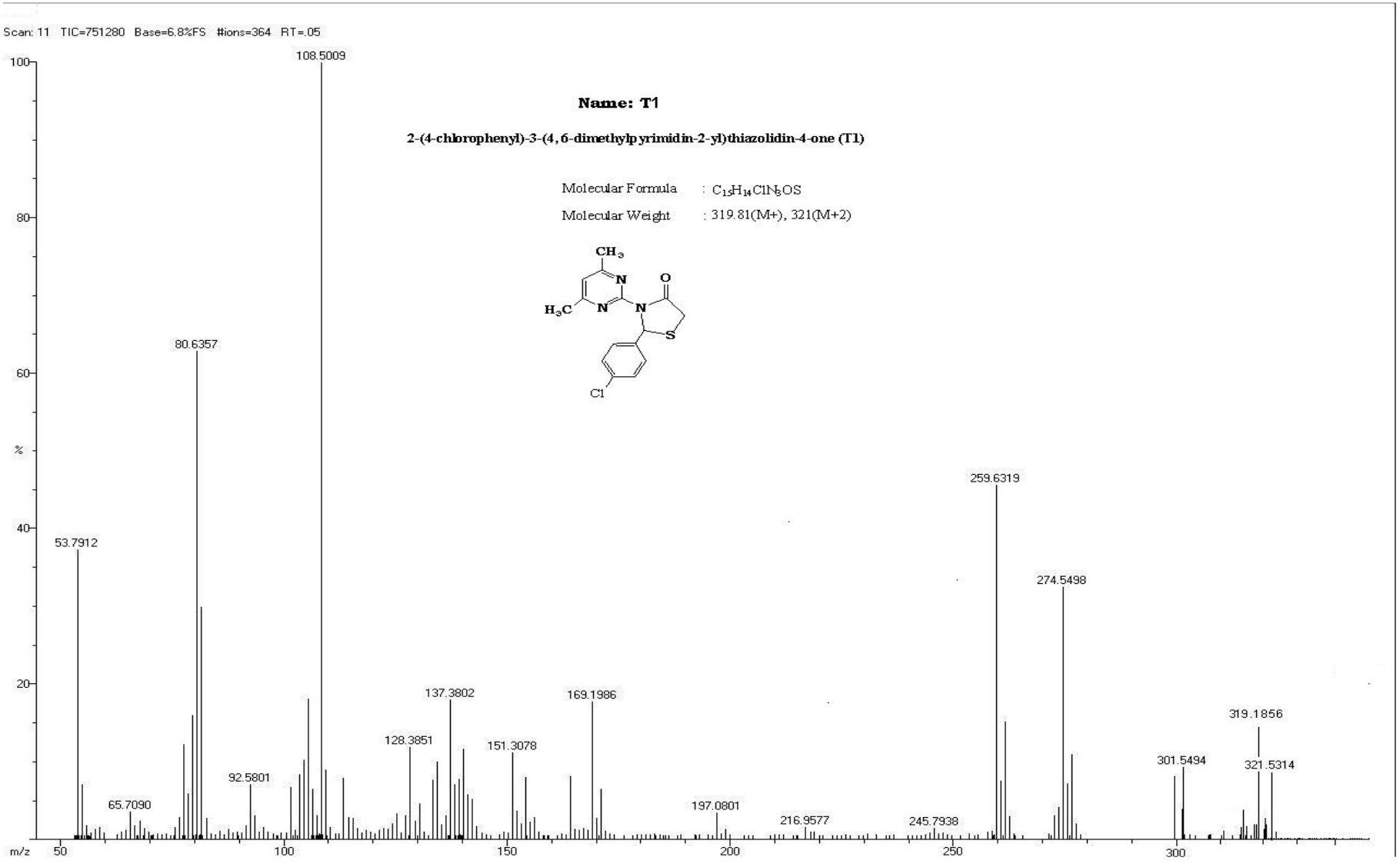
Instrument Type Alpha

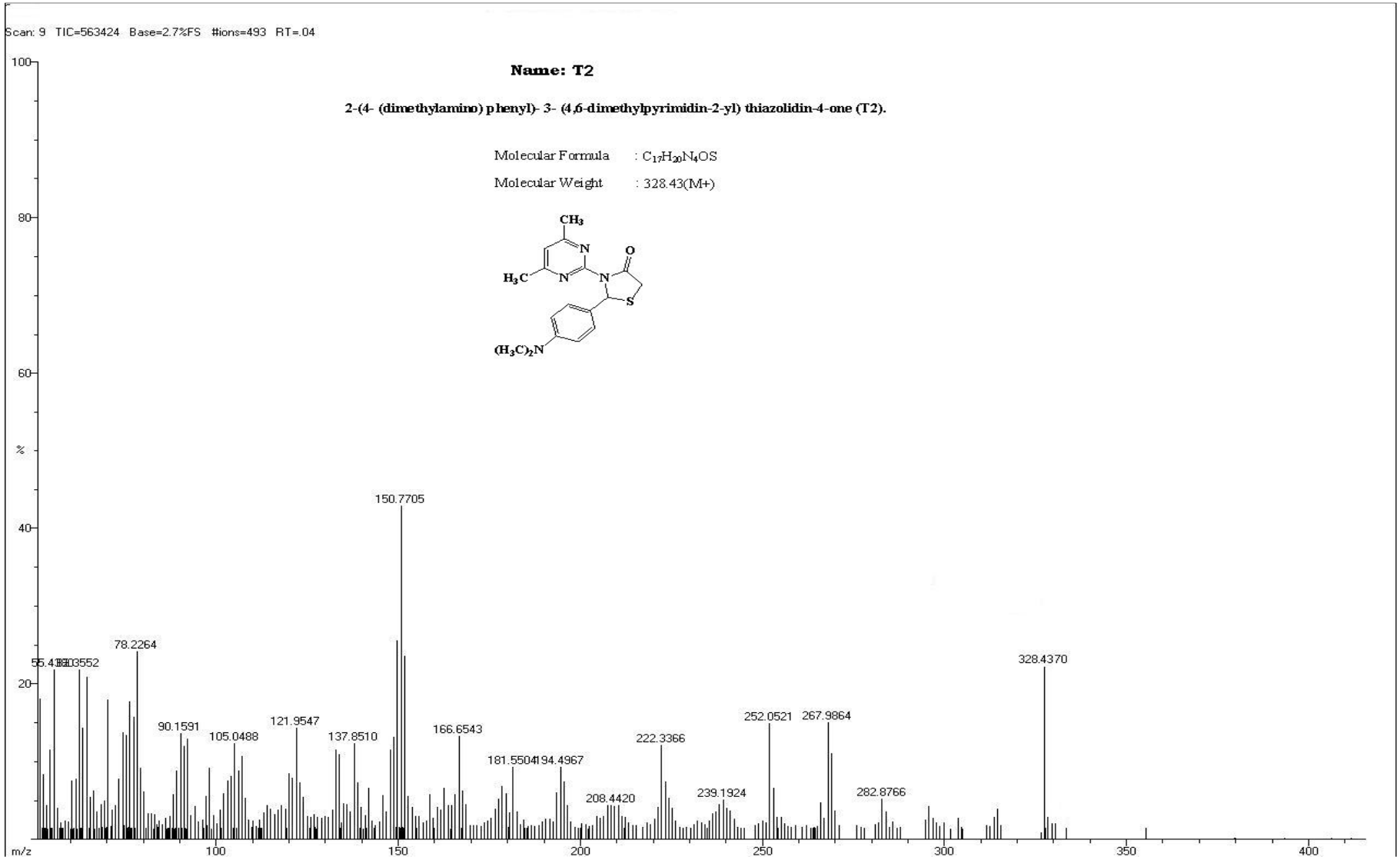
Sample Form solid

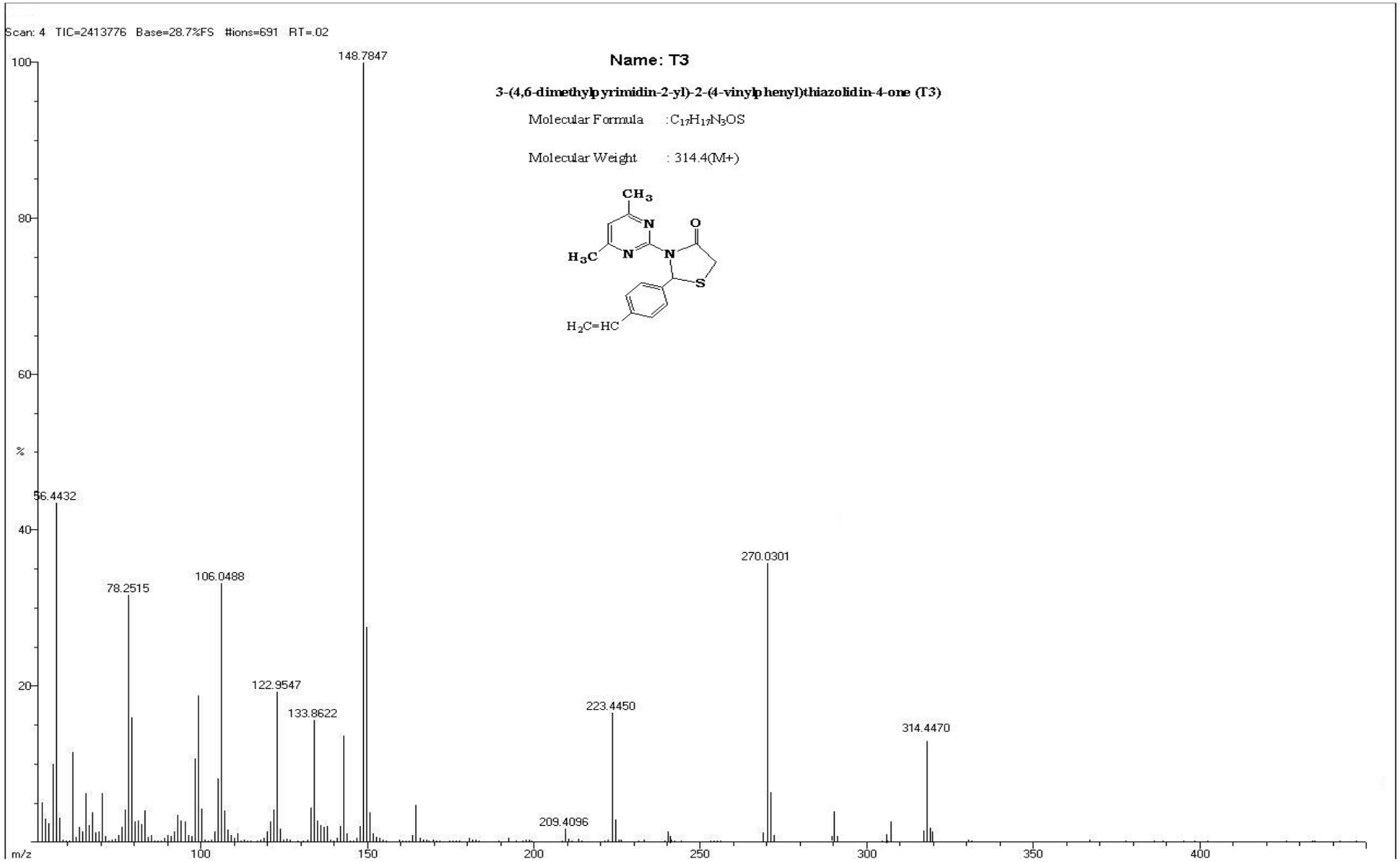
Resolution 4

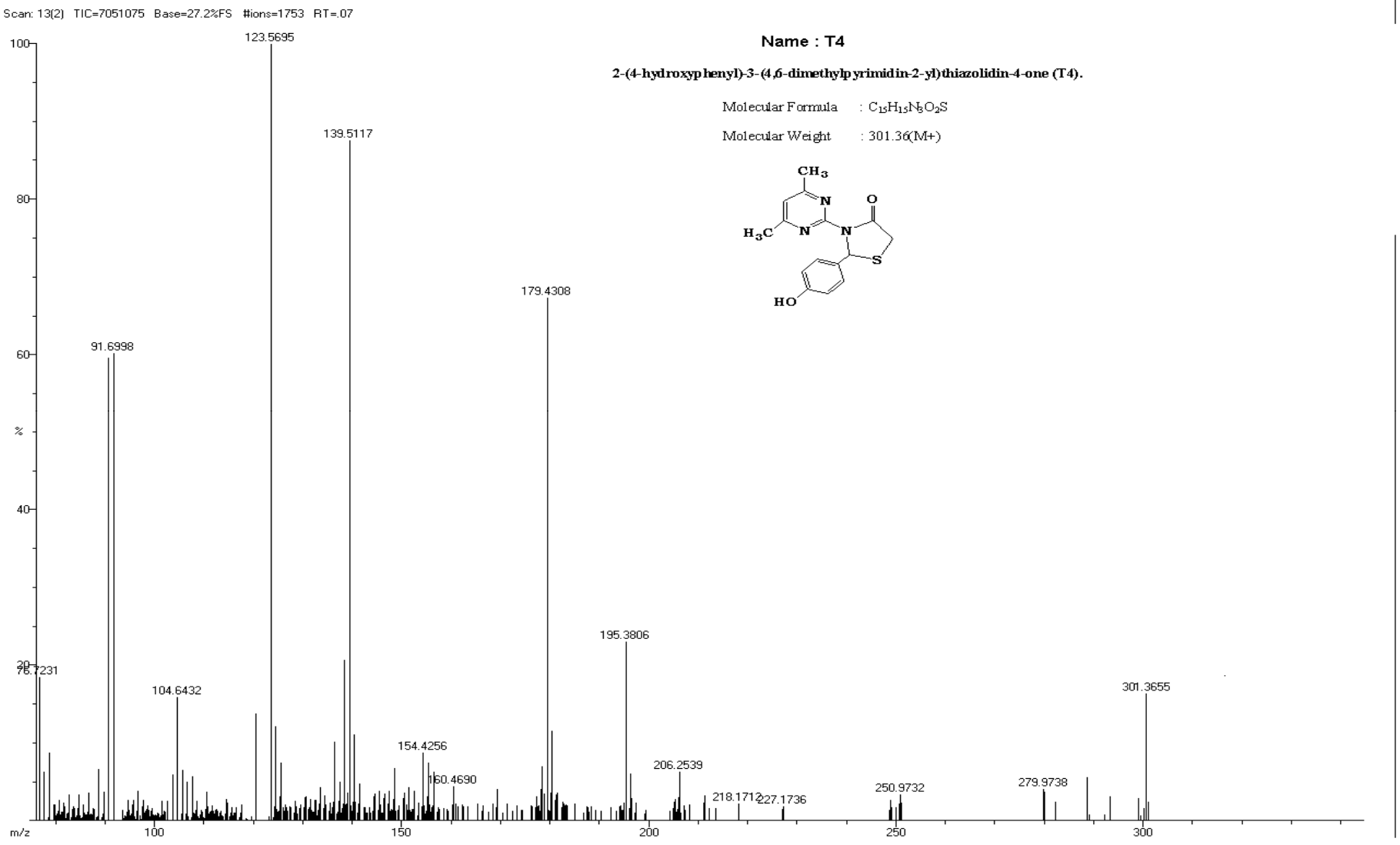
Sample Scans 16

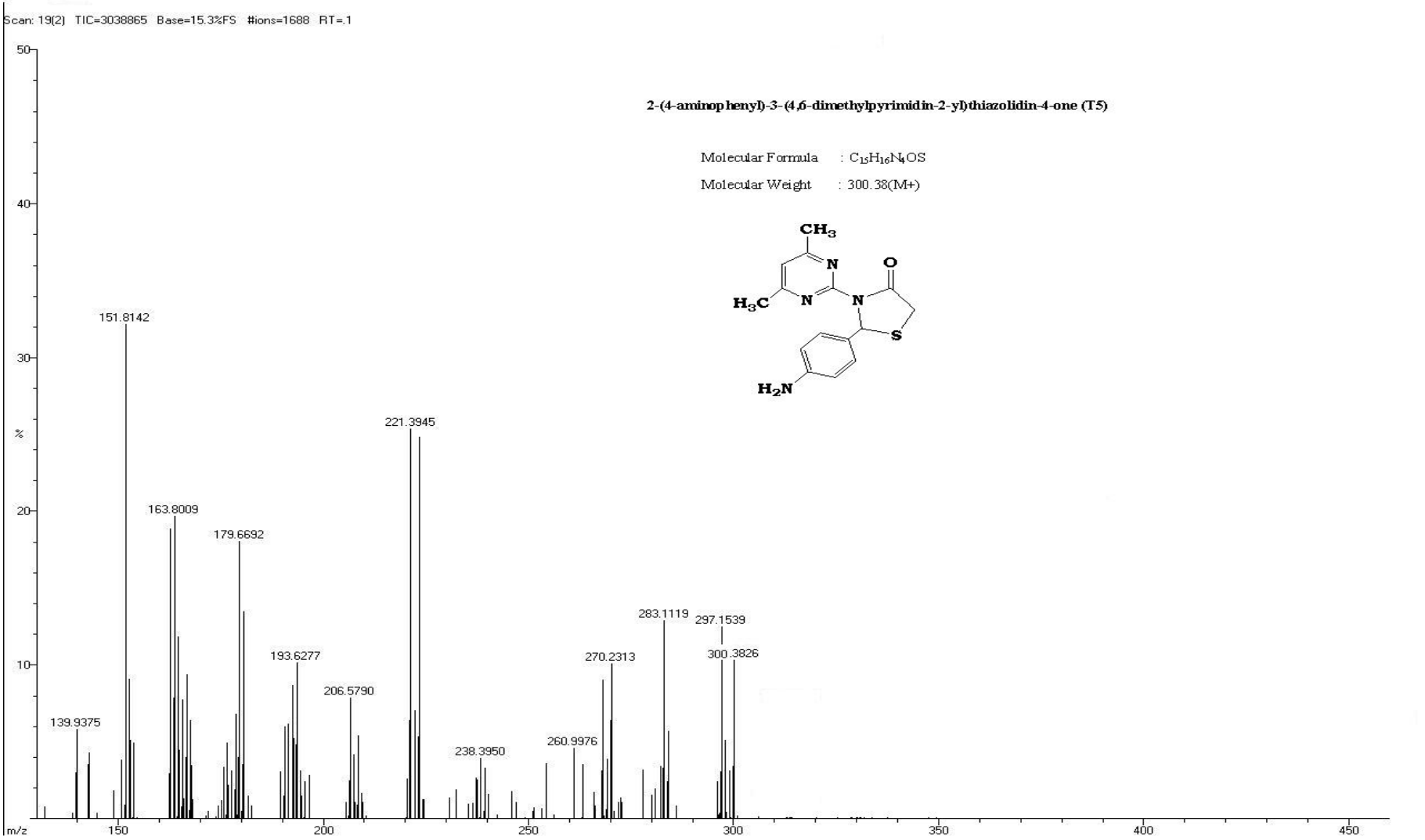
Analyst name: senthilraja


Scan: 11 TIC=751280 Base=6.8%FS #ions=364 RT=.05
Name: T1
2-(4-chlorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T1)
Molecular Formula : C15H14ClN3OS
Molecular Weight : 319.81(M+), 321(M+2)
108.5009
80.6357
53.7912
259.6319
274.5498
137.3802
169.1986
319.1856
128.3851
151.3078
301.5494
321.5314
92.5801
65.7090
197.0801
216.9577
245.7938
%
m/z

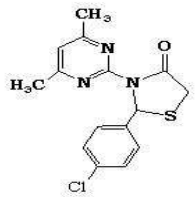

Scan: 9 TIC=563424 Base=2.7%FS #ions=493 RT=.04
Name: T2
2-(4- (dimethylamino) phenyl)- 3- (4,6-dimethylpyrimidin-2-yl) thiazolidin-4-one (T2).
Molecular Formula : C17H20N4OS
Molecular Weight : 328.43(M+)
CH3
N
O
H3C
N
N
S
(H3C)2N
100
80
60
%
40
20
150.7705
78.2264
328.4370
252.0521
267.9864
90.1591
105.0488
121.9547
137.8510
166.6543
222.3366
181.5504
194.4967
208.4420
239.1924
282.8766
m/z
100
150
200
250
300
350
400


Scan: 4 TIC=2413776 Base=28.7%FS #ions=691 RT=.02
Name: T3
3-(4,6-dimethylpyrimidin-2-yl)-2-(4-vinylphenyl)thiazolidin-4-one (T3)
Molecular Formula :C17H17N3OS
Molecular Weight : 314.4(M+)
148.7847
56.4432
78.2515
106.0488
122.9547
133.8622
209.4096
223.4450
270.0301
314.4470
%
m/z


Scan: 13(2) TIC=7051075 Base=27.2%FS #ions=1753 RT=.07
Name : T4
2-(4-hydroxyphenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T4).
Molecular Formula : C15H15N3O2S
Molecular Weight : 301.36(M+)
123.5695
139.5117
179.4308
91.6998
195.3806
76.7231
104.6432
301.3655
154.4256
206.2539
160.4690
218.1712
227.1736
250.9732
279.9738
%
m/z


Scan: 19(2) TIC=3038865 Base=15.3%FS #ions=1688 RT=.1
2-(4-aminophenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T5)
Molecular Formula : C15H16N4OS
Molecular Weight : 300.38(M+)
CH3
N
O
H3C
N
N
S
H2N
%
m/z
151.8142
163.8009
179.6692
193.6277
206.5790
221.3945
238.3950
260.9976
270.2313
283.1119
297.1539
300.3826
139.9375
50
40
30
20
10
150
200
250
300
350
400
450

Compound Name: T1



2-(4-chlorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T1)

BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters	
NAME	Jun25-2018
EXPNO	361
PROCNO	1

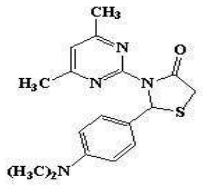
F2 - Acquisition Parameters	
Date_	20100626
Time	12.40
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	296.3 K
D1	1.00000000 sec
TD0	1

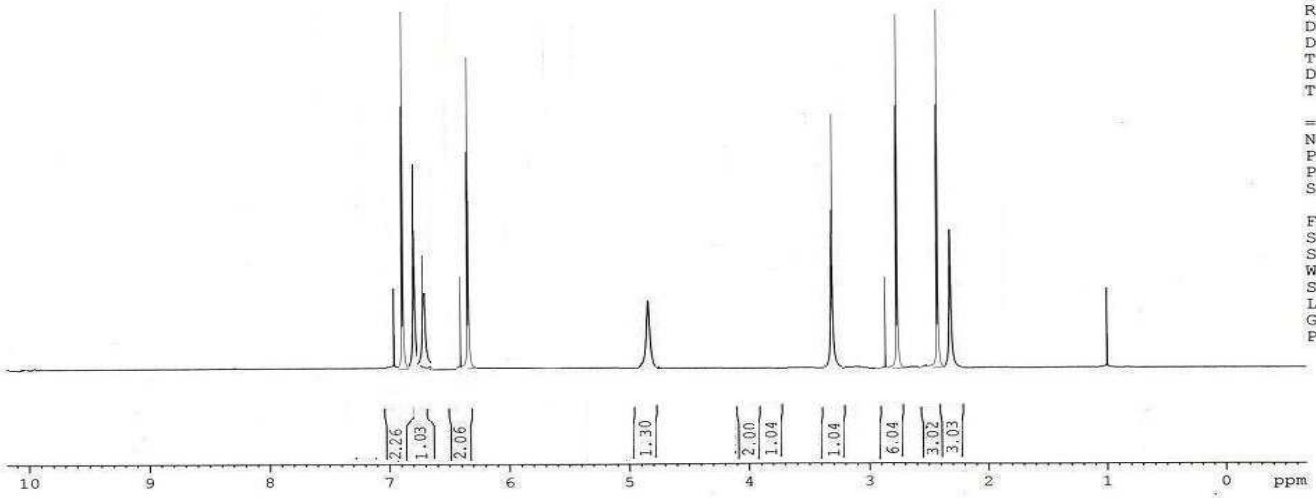
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324008 MHz

F2 - Processing parameters	
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

avtar_saifpu@yahoo.co.in

Compound Name: T 2





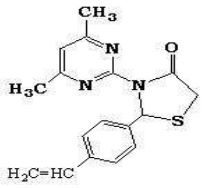
2-(4- (dimethylamino) phenyl)- 3- (4,6-dimethylpyrimidin-2-yl) thiazolidin-4-one (T2).

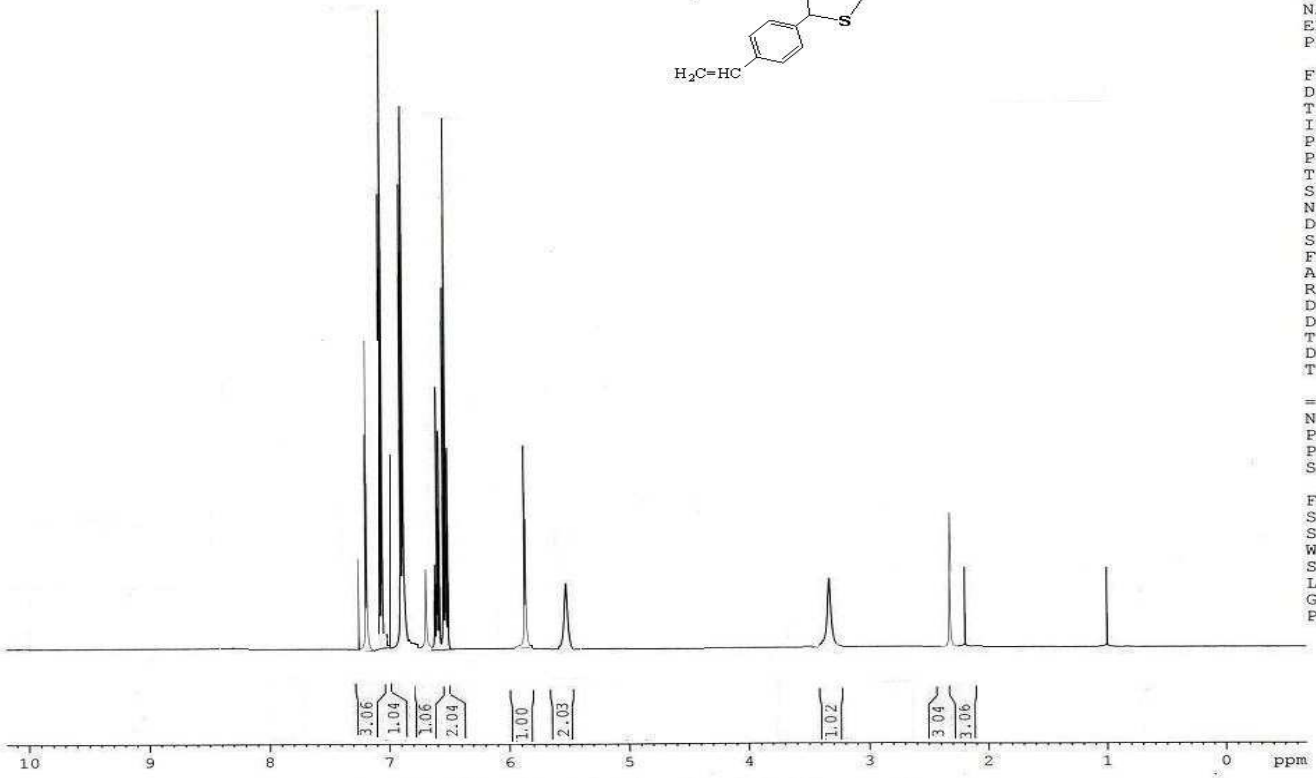
BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters	
NAME	Jun25-2018
EXPNO	359
PROCNO	1
F2 - Acquisition Parameters	
Date_	20100626
Time	13.40
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	296.3 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324008 MHz
F2 - Processing parameters	
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

avtar_saifpu@yahoo.co.in

Compound Name: T3





3-(4,6-dimethylpyrimidin-2-yl)-2-(4-vinylphenyl)thiazolidin-4-one (T3)

BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters	
NAME	Jun27-2017
EXPNO	362
PROCNO	1

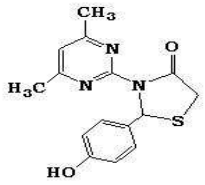
F2 - Acquisition Parameters	
Date_	20100626
Time	13.20
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	296.3 K
D1	1.00000000 sec
TD0	1

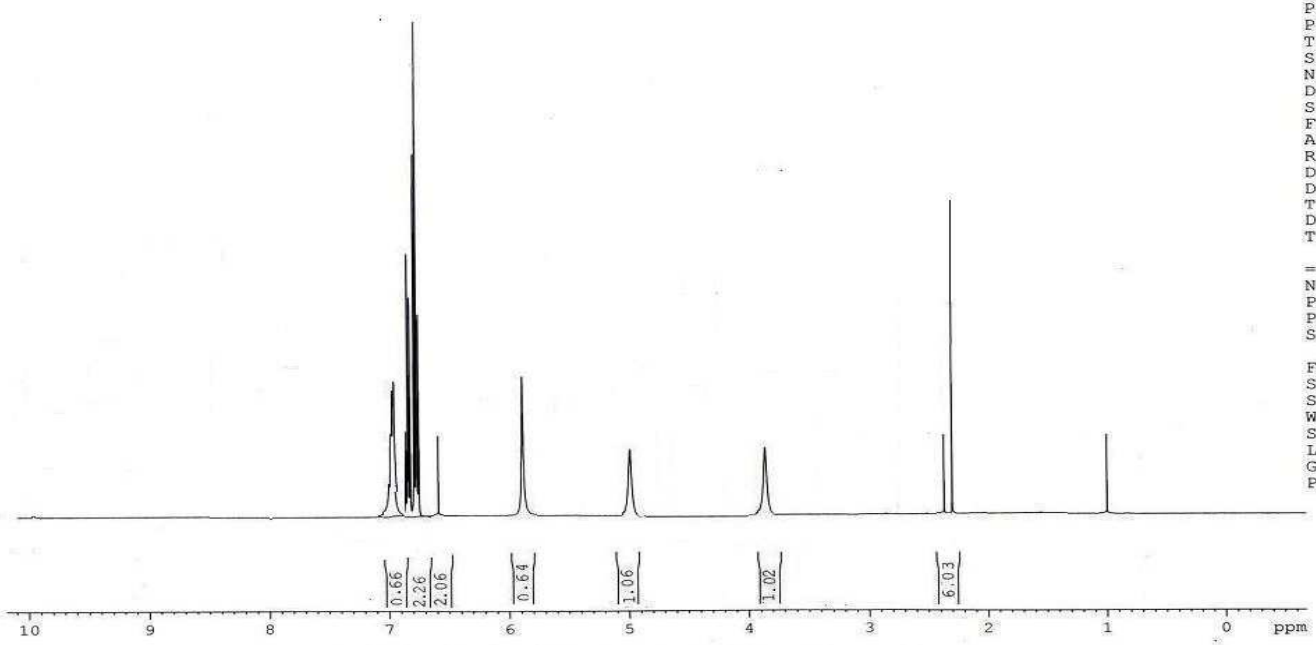
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324008 MHz

F2 - Processing parameters	
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

avtar_saifpu@yahoo.co.in

Compound Name: T4





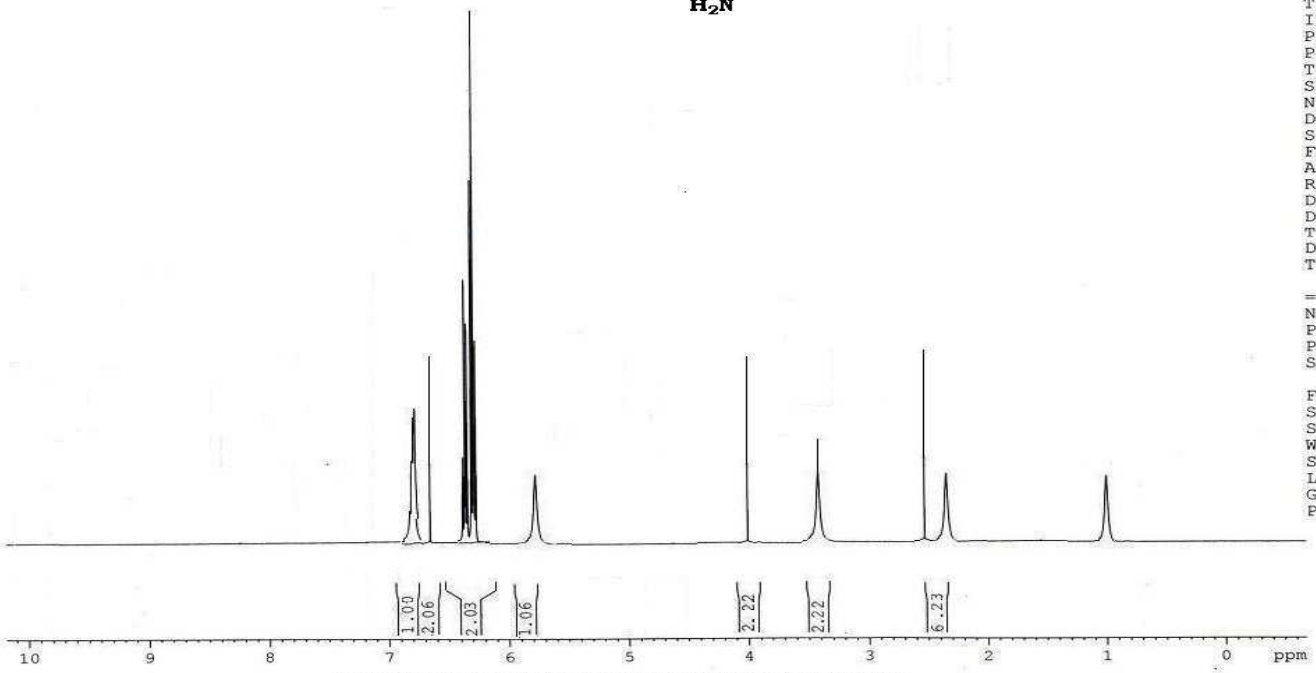
2-(4-hydroxyphenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T4).

BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters	
NAME	Jun27-2018
EXPNO	361
PROCNO	1
F2 - Acquisition Parameters	
Date_	20100626
Time	12.40
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	296.3 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324008 MHz
F2 - Processing parameters	
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

avtar_saifpu@yahoo.co.in

Compound Name: T5



2-(4-aminophenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (T5)

BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters	
NAME	Jun27-2018
EXPNO	361
PROCNO	1

F2 - Acquisition Parameters	
Date_	20100626
Time	12.40
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	296.3 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324008 MHz

F2 - Processing parameters	
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

avtar_saifpu@yahoo.co.in